DEPARTMENT OF HEALTH AND HUMAN SERVICES

U.S. FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION RESEARCH

CELLULAR, TISSUE AND GENE THERAPIES ADVISORY COMMITTEE

Date: October 9, 2009

Time: 8:30 a.m. – 5:00 p.m.

Location: Bethesda Marriott
5151 Pooks Hill Road
Bethesda, Maryland

DR. GERSON: Good morning and welcome. I am Stan Gerson and will be chairing today's session on which we will be discussing a single topic for the Food and Drug Administration, Center for Biologics Evaluation Research, Cellular Tissue and Gene Therapies Advisory Committee, October 9th.

Today, we will be discussing the Isolagen Therapy, BLA, Fibrocell Technologies, and we will conduct this with presentations in the morning and discussion in the afternoon.

I'd like to welcome our audience, our sponsor, and the FDA to this committee session, and our advisory panel, which is made up of current members as well as temporary voting members for today's discussion.

Perhaps what we should do first is go around, and I'll start to my left here, and just let us all know how I would like the introductions to be done, I'll go first.

So I'm Stan Gerson, the Director of the Case Comprehensive Cancer Center and the Center for Stem Cell and Neurodegenerative Medicine at Case-Western Reserve University in Cleveland, and my interests are

in cellular therapeutics, gene therapy, hematopoietic stem cells, and mesenchymal stem cells.

Go ahead.

DR. RAO: My name is Mahendra Rao, and I'm the Vice President for Research and Invitrogen, and I'm the Industry Rep on this committee. I have an academic interest and affiliation with the Buck Institute and JHU, and we work on stem cells, primarily embryonic, neuro, and mesenchymal stem cells.

DR. SNYDER: I'm Evan Snyder. I'm the Director of the Stem Cell and Regenerative Biology Program at the Burnham Institute, also Director of the Stem Cell Research Center. Obviously, my interest is stem cell biology. I'm also a practicing pediatrician, newborn intensivist, and pediatric neurologist.

DR. DUBINETT: I'm Steve Dubinett. I'm the Chief of Pulmonary and Critical Care Medicine, Allergy and Immunology, at UCLA, and I direct the Lung Cancer Research Program in the Johnson Comprehensive Cancer Center. My research interests are understanding the pathogenesis of lung cancer, particularly as it relates to the inflammatory process, and developing therapies

based on that.

DR. WOO: I'm Savio Woo from the Mt. Sinai School of Medicine in New York City. I'm Professor and Chairman of the Department of Gene and Cell Medicine there. My primary research interest is in the area of gene and cell therapy for cancer.

MS. RUE: I'm Karen Rue from Lafayette, Louisiana. I'm the Consumer Representative. I'm with Griswold Special Care.

DR. NEWBURGER: I'm Amy Newburger. I'm a dermatologist in private practice in Westchester County, New York. I have a teaching appointment at St. Luke's Roosevelt Hospital Medical Center.

DR. CHAPPELL: Rick Chappell, Department of Biostatistics and Medical Informatics at the University of Wisconsin Medical School. My interests are clinical trials design and analysis.

DR. DRAKE: I'm Lynn Drake. I'm a dermatologist from Massachusetts General Hospital, Harvard Medical School. I've directed the Clinical Investigation Unit for many years, and I'm currently involved in being the Director of Policy and Planning

for the Women's Center for Photomedicine.

DR. ALLEN: Matthew Allen. I'm Associate Professor of Small Animal Surgery and Director of the Surgical Research Laboratory at the College of Veterinary Medicine, the Ohio State University, and my research areas are pre-clinical animal models for orthopedic spine and orthopedic oncology.

MS. DAPOLITO: Gail Dapolito with the Center for Biologics, FDA. I'm the Executive Secretary for the committee.

DR. KING: I'm Lloyd King. I'm the dermatologist part of this group. I'm from Vanderbilt University. I'm interested in translational research, including mouse models of skin disease, and I'm also very interested in alopecia areata and other hair growth drugs.

DR. TAYLOR: I'm Doris Taylor. I direct the Center for Cardiovascular Repair at the University of Minnesota. I've been involved in cell therapy for about 20 years now, primarily initially in the cardiovascular field, more recently in the hepatic field, as well, and work on tissue engineering as well

as cells and genes.

DR. BURKE: I'm Dr. Karen Burke. I'm a dermatologist. I'm in the Department of Dermatology at Mt. Sinai Medical Center in New York. I have done research on implants and my current research focuses on antioxidants to increase longevity and stimulate the immune system and other good functions.

DR. KWAK: Larry Kwak. I Chair the Department of Lymphoma and Myeloma at M.D. Anderson Cancer Center in Houston, and my research interests are in cancer immunotherapy and cancer vaccine development for hematological malignancies.

DR. OLDING: Michael Olding. I'm Chief of the Division of Plastic Surgery at George Washington University Medical Center.

DR. LIM: I'm Agnes Lim, FDA. I'm in the Center for Biologics, and I'm one of the clinical reviewers for this BLA.

DR. THOMAS: Terrig Thomas. I'm in the FDA, too. I'm at the Division of Cell and Gene Therapies, and I'm the product reviewer on this BLA.

DR. WITTEN: I'm Cecilia Witten. I'm the

Office Director of the Office of Cell Tissue and Gene Therapy, which is the reviewing office in the Center for Biologics for this product.

DR. GERSON: Thank you, all. I'd also just like to acknowledge that both Steve Dubinett and Evan Snyder are now members of our committee, so welcome Steve and Evan to the fray. Thank you.

I'd like to turn it over now to Gail Dapolito to give us a few other comments.

MS. DAPOLITO: Thank you, Dr. Gerson.

I'd like to read the conflict of interest statement for the meeting.

The Food and Drug Administration convenes the October 9, 2009, meeting of the Cellular Tissue and Gene Therapies Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all participants of the committee are special government employees or regular federal employees from other agencies and are subject to the federal conflict of interest laws and regulations.

The following information on the status of

this advisory committee's compliance with federal ethics and conflict of interest laws, including but not limited to, 18 USC 208 and 712 of the Federal Food, Drug, and Cosmetic Act, are being provided to participants at this meeting and to the public.

FDA has determined that all members of this advisory committee are in compliance with federal ethics and conflict of interest laws.

Under 18 USC Subpart 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Under 712 of the Food, Drug, and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the committee their essential expertise.

Related to the discussions at this meeting, members and consultants of this committee have been

screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children, and, for the purposes of 18 USC 208, their employers.

These interests may include investments, consulting, expert witness testimony, contract and grants, CRADAs, teaching, speaking, writing, patents and royalties, and also primary employment.

The committee will discuss Isolagen therapy, sponsored by Fibrocell Technologies, Incorporated, formerly Isolagen Technologies, Incorporated, for moderate to severe nasolabial fold wrinkles. This is a particular matter involving specific parties.

Based on the agenda and all financial interests reported by members and consultants, conflict of interest waivers have been issued in accordance with 18 USC 208(b)(3) and 712 of the Food, Drug, and Cosmetic Act.

Related to Dr. Stanton Gerson, Dr. Gerson’s waiver includes a financial interest in a firm that could be affected by the committee’s discussion. The waiver allows Dr. Gerson to fully participate and vote

on the committee discussion.

Related to Dr. Michael Olding, Dr. Olding's waiver includes a financial interest in a firm that could be affected by the committee's discussion. The waiver allows Dr. Olding to participate fully and vote on the committee discussion.

Dr. Mahendra Rao is serving as the industry representative, acting on behalf of all regulated industry, and is employed by Life Technologies. Industry representatives are not special government employees and do not vote.

This conflict of interest statement will be available for review at the registration table.

We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships

that you may have with any firm that could be affected by the discussions.

In consideration of the committee discussion, we'd also like to ask that you silence your cell phones and electronic equipment, please.

Dr. Gerson, if I may, I'd like to say just a few comments this morning on the passing of one of our former members, Dr. Jonathan Allen.

Dr. Allen was a member and consultant of the Cellular Tissue and Gene Therapies Advisory Committee. He was diagnosed with Stage IV glioblastoma in 2008 and passed away on September 28 of this year.

Dr. Allen was employed by the Southwest Foundation for Biomedical Research in San Antonio, Texas. He was a veterinarian, recognized for his expertise in the area of retrovirology and zoonotic infections. His research contributed greatly to the characterization of human immunodeficiency virus and simian immunodeficiency virus.

He was a valued resource to the FDA as a member and consultant of the Cellular Tissue and Gene Therapies Advisory Committee and its precursor, the

Biologic Response Modifiers Advisory Committee.

He began his service to the FDA in 1995 on the BRMAC. He served on the BRMAC, the Xenotransplantation Subcommittee of the BRMAC, and on the Department of Health and Human Services Secretary's Advisory Committee on Xenotransplantation. He was an active consultant to the Cellular Tissue and Gene Therapies Advisory Committee at the time of his death, having been in service to the FDA for 14 years.

Dr. Allen's expertise on issues related to xenotransplantation was critical to the committee's discussions on issues related to the development of FDA's xenotransplantation policy, including controversial advisory committee meetings concerning the transplantation of bone marrow into an HIV-positive patient and porcine endogenous virus, retrovirus in porcine transplantation products.

He was a thoughtful and independent voice on the committee. He was extremely generous in his service to the FDA and the public health and always made himself available to the FDA when asked. Sometimes his was a minority view in the committee

discussion, but he was always calm and gracious in his remarks. He was a real gentleman and a dedicated scientist and a public servant, and I would like to recognize his contributions to the committee. He will be missed.

If it's appropriate, I'd like to ask for a brief moment of silence, please.

Thank you, Dr. Gerson.

DR. GERSON: We will now move on to our presentations for this morning. We will begin with the sponsor presentations from Fibrocell Technologies.

To help us all keep on our schedule, I would encourage both the sponsor and the committee to allow the presentations to be had and we'll hold discussions until the presentations are completed, so make your notes, and we have a good discussion period after the presentations.

Thank you.

DR. NOVAK: Thank you, Dr. Gerson.

My name is Jeanne Novak. I'm the authorized regulatory representative for Fibrocell. Fibrocell Technologies is a subsidiary of Fibrocell Science,

formerly Isolagen.

Today, our sponsor presentation will include six major talks regarding manufacture, biological effects, early clinical development of the product known as Azfibrocel-T, efficacy results from our two pivotal studies, safety, clinical experience, market context, and post-approval safety assurance.

By way of introduction, again Fibrocell Technologies, formerly Isolagen, is a subsidiary of Fibrocell Science.

Isolagen Technologies was founded in 1994 and is based currently in Exton, Pennsylvania, and has been there since 2005. Fibrocell is a biotech company, focused on developing and commercializing novel autologous skin and tissue regenerative and rejuvenative technologies.

Applications have included treatment of facial rhytids, acne scars, and other tissue regeneration applications. Isolagen reorganized as Fibrocell Science, Inc., in August of this year. Fibrocell Technologies again is a subsidiary of Fibrocell Science.

Today, we'll be discussing Azfibrocel-T. Our USAN name, Azfibrocel-T, is an autologous cell therapy that augments the local population of dermal fibroblasts and is proposed to stimulate the remodeling of the surrounding extracellular matrix. The proposed trade name, although not yet approved by the FDA, will be Laviv.

What is Fibrocel-T? It is indicated today for the treatment of nasolabial fold wrinkles. Azfibrocel-T is a fibroblast cell suspension prepared from the patient's own skin. The cells are viable and replication competent and expressed collagen. Azfibrocel-T is given as a three-dose regimen with a five-week interval between these sessions. Azfibrocel-T is injected directly into the papillary dermis of the nasolabial fold wrinkles.

The indication being considered by the FDA for approval includes Azfibrocel-T as an autologous cell therapy indicated for the treatment of moderate to severe nasolabial folds in adults greater than or equal to 18 years of age.

By way of background, Azfibrocel-T was in fact

marketed commercially as a non-regulated product before the FDA brought it under the regulatory guidelines of the IND. In the U.S., it was marketed between 1995 and ’99, in the U.K. between 2002 and 2007, in Australia and New Zealand 2003 to 2004. Over a thousand patients in the U.S. were treated while it was commercial and over 6,000 in the U.K.

Today, we’re looking at a database of 821 subjects that have been treated under IND for facial wrinkles, who are all included in our Integrated Summary of Safety.

By way of review, Dr. Robert Weiss will be discussing some of our early studies. The focus of the pivotal study discussions is in fact Study 005 and 006. 003-A and B will be discussed by Dr. Weiss. Both of these studies were parallel pivotal studies, as well, and they were conducted under agreement with the FDA under the special protocol assessment, as were Studies 005 and 6.

As you can see, some of the early studies not only included the treatment of nasolabial fold wrinkles but also other areas of the face. And, in fact, as

part of our database, all of these studies and the safety from these studies, regardless of the region of injection, are included in the Integrated Summary of Safety.

We consider Azfibrocel-T a platform technology and it has the potential for multiple indications, and some of the studies that have been conducted under IND have included interdental papillary insufficiency and even vocal cord scarring.

The speakers today will include experts in the area of cell biology, Dr. Lillian Nanney; Dr. Robert Weiss, of course, the past president of ASDS, outgoing this year; Dr. Girish Munavalli; and Dr. Stacy Smith.

In addition to our speakers, we have additional experts on hand to answer questions that may be in the area of expertise for which they specialize. Dr. William Boss is with us today who’s the innovator of the fibroblast transplantation technology, the basis for Azfibrocel-T. Declan Daley is the acting CEO. George DeMuth is a statistician who was involved in the design and analysis of the pivotal studies. Karen Donhauser from Fibrocell is the Director of Quality.

Kevin Hennegan has been in charge of Clinical Operations for the Pivotal Studies and the Acne Scarring Program. Dr. John Joseph, again one of the investigators in the study and a plastic surgeon, as well as John Maslowski, who is the vice president for Operations and can answer any questions regarding manufacturing.

With that, I'd like to move on to a brief overview of the manufacture of Azfibrocel-T.

At a very high level, the overview is fairly straightforward. Skin biopsies are required from behind the ear of the patient. The biopsies are transported under special conditions to the manufacturing facility where cell propagation occurs.

The average time for cell propagation proper is 50 days. Cryopreservation of the patient's cells occurs. We call this the drug substance cryopreserved product. Release testing is performed at this juncture. If release testing is adequate, the cells are considered suitable for reinjection into the patient, and at the time of scheduling of a patient, the material can be thawed, prepared for injection, and

shipped directly to the clinical site.

A 3 millimeter punch biopsy is actually removed from behind the ear, again going to the manufacturing facility. Fibroblasts are isolated and multiplied into tens of millions of new cells, again a micrograph of fibroblasts in culture and adherent to the culture vessel, and at the end of the propagation period, cells are harvested.

Again at this stage, there is release testing that occurs in order to deem the product adequate for use in patients. The release testing that occurs on the drug bulk substance cryovial includes cell count, viability, purity and identity, microplasma testing, endotoxin, and sterility. And as a note, the specification for purity of fibroblasts is greater than or equal to 98 percent.

At the time the drug substance is thawed from cryopreservation and prepared for injection, the following occur. The cells are thawed and washed extensively to yield the patient-specific Azfibrocel-T product. The Azfibrocel-T is then packaged as a sterile product and shipped overnight at 28 degrees in

validated shipping packages.

Autologous cells upon receipt are prepared and then injected into the treatment area, nasolabial fold wrinkles, where they are believed to produce organized extracellular matrix proteins, and, again, that includes collagen. And, in many ways, we see this process somewhat analogous to a natural wound-healing process.

The release specifications for the actual vial of material that goes to the patient directly includes, again, cell count, cell viability, collagen content, gram stain sterility, and endotoxin testing.

So the manufacturing time thus far has averaged about 50 days in culture, and let me explain. The culture time includes from the time the biopsy is received at the cGMP facility to the time that several passages have occurred and increasing numbers of cells have been acquired to the day that we call harvest.

In the 005 and 6 studies, our minimum time to harvest was 36 days, our maximum was 71 days. This represents the autologous nature of our product and that for each lot, each patient generates their own lot

and there is subtle variability between the time for culture.

Eighty percent of the lots turned out that they were manufactured or went to harvest in less than 55 days and only eight lots took greater than 60.

Before release to the clinic, however, there is four additional weeks of testing, so 50 days in culture plus the four weeks of testing, is approximately 90 days to return the product to the patient in the clinic.

As an overview, each Azfibrocel-T dose is actually two vials of drug product, the Azfibrocel-T drug product, and each of these vials contains 10 to 20 million cells per ml, again shipped overnight and can be used the next day or up to 48 hours. Each dose or two vials is used to treat up to 20 linear centimeters of nasolabial fold wrinkle, and the injection volume per injection site along the nasolabial fold, which will be described in more detail by Dr. Munavalli, is .1 mls per centimeter.

I'd now like to introduce Dr. Lillian Nanney from Vanderbilt to discuss the biological effects of

Azfibrocel-T.

DR. NANNEY: I'm Lillian Nanney. I'm a professor in the Department of Plastic Surgery, Cell and Developmental Biology, at the Vanderbilt School of Medicine, in Nashville, Tennessee.

I'd like to begin by declaring that I've had no prior association with Fibrocell or any other products that might be competing with that product. My support to this meeting, my travel, lodging, and compensation for the day have been provided by Fibrocell. I was selected for this because I'm an expert scientist in the wound-healing field and there's some aspects of that that are germane for this proposal.

My talk is divided into four segments and we will begin first with the structure of normal as well as aged skin. This is a histological view of normal skin. You will notice on the outer purple layer we have a stratified squamous keratinizing epithelium which serves as the barrier function for the skin, the outermost layer.

Beneath that, we have a pink layer, light pink

and more intense pink. This is the dermis. This is the region of interest for this proposal. You will notice, if you look carefully, that there is a pale area near the surface of the epidermis. This is labeled the papillary dermis. The collagen fibrils there are loosely organized and not as cross-linked as they are in the more intense pink, area which is the lower region known as the reticular dermis. The arrow over here indicates the target zone for the injection of the Azfibrocel product.

This image is included to highlight the cell of interest today, that is the fibroblast. It is the most predominant cell in the dense irregular connective tissue known as the dermis. These cells are suspended in a 3-dimensional matrix which consists of many cables and fibrils shown here. Most of these are Collagen Type I with a minor contribution from Collagen III.

There are other additional fibrillar and non-fibrillar collagens present. The fibroblasts are very busy secretory cells. They also make elastin fibers. They make molecules, such as hyaluronic acid, to fill in the spaces of the matrix. And in situations in

wound repair, they make enzymatic materials, such as matrix metalloproteinases, the one most familiar to you might be known as collagenase.

But that was normal skin and today we're talking about patients that have aged skin, that have some difficulties with their aged skin, such as loss of elasticity, thinning of the dermis, a decrease in the collagen and elastic fibrils, the abundant fibroblasts become less abundant and become depleted and some actually become senescent; thus, the dynamic equilibrium between collagen synthesis and collagen degradation is altered in these patients.

You're all familiar with other aging phenomena where similar things happen, such as osteoporosis, where bone breakdown exceeds new bone formation and putting patients at risk for fracture. In the case of aged skin, patients become at risk for wrinkles, sagging, and loss of elasticity in their skin.

Now for the proposed biological effects of Azfibrocel-T, this is a rather unique product. As was mentioned earlier, it's been already tested in the human model, some 7,000 plus patients before coming

before the FDA here. So there's a paucity of studies to actually nail down the biological effects that we have many patients to go on and suggest the following.

Intradermal-injected autologous fibroblasts replenish dermal fibroblasts that are depleted in aged skin. We think these are active cells that produce collagen and other extracellular matrix components, like they normally do, and we propose that the fibroblasts stimulate remodeling of the extracellular matrix that is analogous to the fibroblastic activity that's present in the normal wound repair process. And so I'd like to briefly overview the normal wound-healing process because it is germane to this presentation.

As you can see in the top graph here, the wound-healing response is a three-part process, if you look at it in a simplistic fashion. There's first the inflammatory phase, which is always incited following any either mild or severe injury. There's a cell proliferative phase, and wound-healing proceeds normally toward maturation.

The fibroblasts, shown in red, peak after

several days of wound repair and then they diminish in their numbers. You can see on the lower graph that these are a few of the products that are made by fibroblasts. I'd like you to notice the most prominent product which is the Collagen Type I and how it increase in a linear fashion in response to wound repair. So those are the kind of quick view of wound repair.

Wound repair has a conclusion. As time goes on, fibroblast remodeling is self-regulated and self-limiting. The inflammatory populations diminish in the absence of an infection. Fibroblast proliferation slows, cells become relatively quiescent. There are other cells that are present and stimulated by wound repair, such as capillary endothelial cells. They undergo apoptosis and so things diminish in the wound. Collagen synthesis slows and the collagen fibrils assume a close to original basket weave architecture.

The reason we're talking about wound repair is that the needle injection of any of these fillers or cosmetic things that are introduced into the skin must be introduced with a needle. That has to slightly

injure the skin by poking the needle through there. And so a small wound is created and this stimulates a modest wound-healing response to the Azfibrocel-T.

Injection of autologous fibroblast, as you can see, goes into this target area between the papillary dermis and the reticular dermis, leaving behind a trail of fibroblasts that then begin to proliferate and secrete their products and become spaced out.

I'd like to talk about the potential for scar formation. All anesthetic and cosmetic products, as I mentioned earlier, are administered by intradermal injection and this creates a small associated risk of scar formation for all these products.

Now we're all familiar with the excessive collagen production and decreased collagen degradation by fibroblasts that's associated with abnormal scar formation.

Patients are known to form hypertropic scars and actual keloids in response to major injury, linear incisions, lacerations, and excisional wounds, as well. But with Azfibrocel-T, the risk of scarring following treatment is considered low, based on the following

circumstances.

As we all have experienced many wounds in our bodies throughout our lifespans, we know that wound healing is self-limiting in most cases. The use of fine-gauge needles will be used with this product to minimize tissue injury, and the clinical experience on over 7,000 patients to date indicates that the risk of scarring is very minimal.

This risk is further mitigated by the fact that this product will be injected along wrinkle lines. These are well known to be lines where there is diminished skin tension and fibroblasts are less responsive when they’re not under tension and pressure. So this is likely to lead to decreased scar potential.

Patients who would receive such therapy would have certainly had experience enough to know whether they have developed a history of keloids previously and will be counseled not to participate.

Lastly, I would like to end with one of the basic science studies that I have selected. It is the one that is most relevant. It appeared last year in the Chinese literature. This group has no association

with the Fibrocell company.

They were a very astute group. They picked a model that would challenge the product the most. They cultured autologous fibroblasts through four passages, very similar to the method of manufacture used by the company. They injected the product into the right ear of New Zealand white rabbits and they used a saline placebo into the other ear. This was a good model because the rabbit ear model is one of the only ones that is known to have hypertrophic scar formation. This animal model has been popularized by Tom Mustoe and associates and is well established.

The group administered three 1 ml doses to the ears at intervals of two weeks. In addition, they radio-labeled some of the fibroblasts so that they could see and do cell tracing studies. They let the study run for five months and the areas of injection were then excised and evaluated for histology.

By gross visual examination after five months of receiving injection, the injected areas entirely resembled normal adjacent skin. They were without bumps, nodules, or any evidence or hypertrophic scar

formation. And in those few rabbits that received the radio-label tritiated thymidine experiments with the fibroblasts, these fibroblasts were found to persist at the sites where the injection was made for at least five months.

They also looked to see that not only were the cells present but were they also doing their normal secretory activities. They looked at Collagen I. Levels were identical in both the ones that received the saline injection as well as the ones that received the product, but they did notice a difference. They noticed an increased level of Collagen Type III in these tissues. After five months, they saw no abnormal growths or tumors, either visually or histologically.

So, in conclusion, the biological effects of Azfibrocel-T are proposed, based on the host of evidence we've seen. We believe that this product mediates the skin repair by deposition and organization of new extracellular matrix components. The cultured fibroblasts can survive for a period of many months following the injection, and the biological effects of Azfibrocel-T augment the normal process of wound

healing and achieve meaningful clinical responses that you're about to see in the subsequent speakers.

Our next speaker will be Dr. Robert Weiss, who will talk about the early clinical development of Azfibrocel-T.

DR. WEISS: Good morning. My name is Bob Weiss. I'm a dermatologist in private practice at the Maryland Laser Skin and Vein Institute in Baltimore. I'm also an associate professor of Dermatology at Johns Hopkins part-time and have just served as president of the American Society for Dermatologic Surgery.

I'm here today because I was a principal investigator in the Fibrocell, formerly Isolagen, Clinical Studies 002, 003-A 003-B, and the newest one, the 008, the acne scarring.

I do not have any significant or any equity position with Fibrocell. We do a lot of clinical studies and we do have affiliations for studies with competing companies, and Fibrocell has paid my travel and lodging to this meeting, and I'm being compensated for my time out of the office today.

So as kind of a little bit of a history of

which you may not have received information, although you probably did, I'm going to go over the early clinical studies 002 and 003.

These are the studies going back to the first study. I was not involved with the first study but I was involved with 002, which allowed us to do equal numbers of patients for nasolabial folds, melolabial folds, acne scars, and pockmarks. Even though we were allowed to do glabella, we didn't do much. We had a 111 patients treated and the vehicle served as the control.

In the 003 studies, by FDA/SPA agreement, we did more equal numbers of control with the vehicle versus treated patients, and I'll go over a little bit more of the details.

Basically, this product, Azfibrocel-T, as it's now known, has been injected in many different areas of the face when it was on the worldwide market, as well in the U.K. People were injecting it not in specific protocols but pretty much there are records of almost every region of the face.

In the studies, as we look here, most of the

studies have been done on the nasolabial folds and there were a few patients in the trial in glabella and certainly acne scars on the cheek, of which I'll show you a very few examples.

The technique, as has been described this morning and it's akin to the technique since I've been around since the development of Zyderm and Zyplast, those bovine products, basically it's similar injection technique where the needle is advanced. We try to get in the upper dermis where we can still see the needle through the skin and then, as we withdraw, leave a small trail of these fibroblasts.

The worldwide exposure has been over 7,000 patients treated worldwide and the records indicate that there has been subject satisfaction with treatment consistently positive across all studies.

Let's go on. As we review the 002 study, this is a 151 treated subjects, the dose involved 2 million cells per ml with up to 2 mls per treatment. The treatment interval was three treatments at two to three weeks apart, and the primary efficacy time point was three months after the last injection, and that was

initiated in May of 2003.

The efficacy assessments included an internally-developed 7 point wrinkle severity scale with a photo guide. Response time is defined as one point improvement in the primary treatment area, and at that time using Visual Analog Scale for subject assessment of wrinkle severity. I know in these days studies don't really rely on that, other than for pain assessment.

The clinical outcome in the 002 study was that the product was statistically superior, both in response by investigator, live assessments and subject assessments, positive safety profile with very mild-moderate, very short-lived injection site reactions. And at that time I felt compelled to put this in the literature. It was a long process since many of the peer reviews did not know about this product at all, but we did get it published.

Here are some examples from that 002 study. Many of these patients I still see for their routine and cosmetic dermatology treatments, so I've had long-term follow-up with these patients. And I think I will

show you that in a very brief talk later.

We had excellent response with acne scars. I just spoke to this gentleman. He now lives in Texas, and if he didn't live in Texas, he would have come in and I would have had a photograph of what he looks like today. But he's been doing very well, and that was a picture published in that study.

In the 003-A and B groups, we had six U.S. sites. We had 48 treatments, 59 vehicle control, 52 in the B and 52 vehicle control. These were for nasolabial fold wrinkles and glabella, glabellar lines. And I believe to be in this study you had to have both.

Treatment dose was identical to the previous study and the treatment interval was a little bit shorter, three treatments, and the efficacy time point was six months after the first injection, and that was initiated in July of 2004.

The co-primary endpoints, as agreed to with the FDA under the SPA, was a mean change in the subject VAS assessment of primary treatment area and proportion of responders, greater than two point improvement, based on the investigator live assessment of primary

treatment area.

Now what was the scale? I will show you that in a moment. It's a validated 6 point Lemperle scale and the subjects did their Visual Analog Scale. So this was the scale that we were dealing with in the 003 studies and we had to achieve a two point improvement.

As you can see, for those of you of my colleagues who I recognize and know do fillers on a regular basis, you'd understand that there's sort of an etched-in line as well as a fold which comes from a descending malar pad on the upper cheek. And that can sometimes for an inexperienced investigator, a photo assessor, make a difference. But, generally, in all the studies that we do with fillers, it's easier to get from a Grade 3 to a Grade 1 than it is from a Grade 5 to a Grade 3.

So in review of the data, and again with that proviso about the photo scale that we were using and the investigator live assessment, the B arm was statistically significant for an investigator live assessment and statistically significant for subject live assessment on both arms of that 003 study.

So the conclusions and sort of the set-up for the pivotal studies that we're going to be discussing in detail momentarily, Azfibrocel-T is safe for treatment of facial wrinkles and scars. I've had very long-term experience with it. There are temporary injection site reactions which we will detail and those are the most common adverse events.

The product is efficacious at improving the appearance of facial wrinkles when administered at this dose, at .1 ml per linear centimeter of wrinkle. The pivotal studies designed to improve the consistency between clinical sites and the capacity to measure clinical effect with statistical significance. So I think that was a very good set-up for that.

To talk to us about the pivotal studies, the 005 and the 006, I'm happy to introduce my colleague Dr. Munavalli who first got involved in some of these clinical trials while he was doing a fellowship in my office and so it's a pleasure to see him.

DR. MUNAVALLI: Thank you, Bob, and good morning to the advisory panel members, fellow colleagues, and others in attendance today.

My name is Dr. Munavalli, again, and I'm a board-certified dermatologist and fellowship-trained surgeon for the treatment of skin cancer, and I practice as the medical director of Dermatology, Laser and Vein Specialists of the Carolinas in Charlotte, North Carolina, so greetings from the South. I'm also an associate professor part-time at Johns Hopkins University in the Department of Dermatology.

I was asked to speak today, as Bob mentioned, because I have experience as a sub-investigator with RT003 as well as the principal investigator for 005, which we'll talk about, 007, which is panfacial augmentation for skin rejuvenation using Isolagen, Azfibrocel-T, and 008, which is targeted use of Azfibrocel-T for the treatment of acne scars.

I do not have any significant equity position with Fibrocell. Since I spend about 20-25 percent of my time doing clinical trials, we do work with other competing companies with devices and with other injectable products. Fibrocell has paid for my travel, lodgings, and is compensating me for my time today.

Okay. So today we'll talk about the efficacy

of 005 and 006, first beginning with the study design.

By way of the study design overview, there are two identical multicenter randomized double-blinded vehicle controlled studies, 005 and 006, which went on virtually simultaneously. 005 had 203 subjects at seven sites and 006 had 218 subjects at six sites.

During these studies, three administrations of the product or vehicle were administered bilaterally to nasolabial fold wrinkles. The co-primary endpoints were evaluated at six months after the first treatment. The subject, injecting physician, and the evaluator were all blinded.

Let’s look at the co-primary efficacy endpoints which, as we know, statistical significance for both of these primary endpoints must have been met to achieve success for this pivotal study.

The subject live wrinkle assessment was a two point improvement on wrinkles at the lower part of the face on a 5 point scale, and this was done at the six-month follow-up visit. The evaluator live wrinkle assessment was a two point scale, a two point improvement on the 6 point Lemperle scale, which you’ve

just seen, for bilateral nasolabial fold wrinkles, both right and left, at six months, as well.

There were some secondary efficacy endpoints included, the first being a two point move on the subject and evaluator live assessment scale, not at six months but at visit three, four, and five, which were two months and four months, and improvement in the subject and evaluator photographic assessments comparing the photographs at visit baseline, at the following time points visit three, four, five, and six.

Let’s look at a little bit more at the endpoint assessment scales. I just mentioned the subject live wrinkle assessment and mentioned also the lower part of the face.

If you look in the diagram below, referring to the wrinkles below the dotted line, and that is primarily the nasolabial fold and some might call the melolabial portion, the melolabial or the marionette lines. The subjects were asked how they felt about these wrinkles, and had to grade themselves on the scale listed here, and they had to say they were either very satisfied or dissatisfied to qualify.

The live assessment of the way this was conducted, live assessment of those wrinkles we just showed you on the lower part of the face were done in the clinic and they were done before the evaluator live wrinkle assessment at baseline treatment, baseline treatment three at month two, month four and month six.

Now, let’s look at the conduct, how we conducted the evaluator live wrinkle assessment. Again, this was done also in the clinic, but this was done after the subject assessment. It’s also done at the following intervals, baseline, treatment three, month two, month four, and month six, and again both right and left nasolabial folds were scored separately. This was performed by a separate blinded evaluating physician who was not the injector. And, again, as we saw before, the Lemperle scale was used as the photo guide for this.

Let’s briefly touch on some of the eligibility criteria for enrollment. The subjects must have been graded as a 3, 4, or 5 on that scale by the evaluator for each nasolabial fold independently. The subjects must have scored themselves, as I mentioned, as either

dissatisfied or very dissatisfied on that subject assessment scale we just saw. There should be no excessive dermatochalasia or sagginess or laxity of the nasolabial fold area, which would impinge proper grading on the Lemperle scale.

The total treatment area must not have exceeded 20 centimeters in length. No permanent or semi-permanent fillers would have been used for at least one year prior to enrollment, and no excessive exposure to sun or sunburn in the post-auricular area where the biopsies were taken.

These pie charts just demonstrate the subject live assessment at time of baseline. You can see that it’s roughly the same for Azfibrocel-T and the vehicle. Thirty-six percent were dissatisfied for the product, 42 percent for the vehicle, and 64 percent were very dissatisfied that were in the product group, and 58 percent in the vehicle. And the same pie chart for the baseline evaluator live wrinkle assessment, again, very similar. Forty-seven percent of the evaluators graded the baseline wrinkles as moderately deep at 40 percent as deep in the product versus 46 and 42 percent in the

vehicle.

The combined demographics, if you combine the cohorts, 005 and 006, you get a better idea of the range in terms of gender and ethnicity. So in terms of gender, very similar distribution between the product and the vehicle as well as age. In terms of race and ethnicity, we have added a column to your far right, which is recent data from the American Society of Aesthetic Plastic Surgeons. And these are groups of individuals that have come in for treatment or are interested or have actually had treatment or cosmetic procedures, and looking at the percentages and the breakdown, especially with regards to race and ethnicity.

So we can say with regards to the vehicle and the product itself, very similar distribution. In some cases, they were lower, as in the case of African Americans, but in some cases it was higher, as in the case with Hispanics, and Hispanics were, I believe in the surgery, the fastest-growing segment of the population who had achieved treatments.

Let’s look a little bit at the injection

technique, which was described but in detail here. You'll see that the injection needle, the device was actually standardized. It was a 29-gauge, 12.7 millimeter beveled needle on a 0.5cc syringe, and that was used for all injections.

The injections were targeted, as we've seen, in the papillary dermis of the skin with the bevel facing upwards. The injection volume consisted of 0.1 milliliters of Azfibrocel-T into that target area and this resulted in an immediate endpoint for the injector which included mild blanching and the development of a temporary bleb.

This blanching was really a key indicator for being in the correct injection plane, as I'll show you in the next slide.

About 6 to 10 injections were distributed along each nasolabial fold. And here we can see the arrows pointing to the orientation. There's a linear threading technique used where the arrow, the tail of the arrow is where the needle was inserted and the head is where the injection actually began, and then serial threading backing in a retrograde fashion.

When injected properly, you can clearly see a nice blanching that occurs in the area here immediately following injection, and this process was continued all the way down the crease of the nasolabial fold.

So some of the primary efficacy in 005 and 006, first looking at the study design, this was looking specifically at the study sample size and power.

The expected response rate of a two point improvement on the Lemperle scale, based on 003 and 003-A and 3-B experience, was greater than 40 percent respondents for the product and no more than 20 percent for the vehicle control. An overall output level of 0.05 with a two-sided comparison required a sample size of 82 subjects per arm to achieve an 80 percent power using the normal approximation for the binomial. Approximately 100 subjects per arm were enrolled in this study.

Let’s define the study population a little bit more in detail. The ITT or the intent-to-treat population included all randomized subjects, regardless of whether they received any study treatment

injections, and the numbers are listed here.

The other population was the MITT or the modified intent-to-treat population, and those were subjects that received at least one injection during the study.

Okay. Looking at the subject live wrinkle assessment at visit six, it is a primary efficacy endpoint for the ITT population. You can see a comparison between the two cohorts, 005 and 006, highly statistically significant, with percent responders being in the 005 57 percent versus 30 percent for the vehicle, and 006, it was 46 percent versus 18 percent for the vehicle. Again, note the extreme statistical significance.

In the evaluator live wrinkle assessment, again for the same time point, visit six, in the ITT population, you can see for 005 and 006 the values listed here. The percent responders for 005 33 percent versus the vehicle 7 percent and for 006 it was 19 percent versus 7 percent for the vehicle.

So we were held to a high standard of a two point move in the Lemperle scale, and fully a third of

the respondents in the 005 achieved statistical significance, which is again very impressive.

With regards to disposition or discharge from the study, these are some of the reasons listed here as you can see in this table. Of note, none of the study subjects were discharged based on adverse events related to the treatment, and most patients were discharged prior to their first treatment.

Let’s look at the secondary efficacy endpoints, and these were again at time points other than or including visit six. This was a subject scale, which was again a two point improvement, showing the gradual improvement from starting as early as visit three and going all the way out to visit six. And you can see the vehicle versus Azfibrocel-T.

Of note also is the increase in response with regards to the vehicle at each time point. And for those who evaluated fillers and looked at those in previous studies and the previous panels, this is a little unusual because most of the time the fillers begin to show some narrowing of that gap whereas here we have a widening of the gap, which suggests increased

improvement over time.

The same here. This is the evaluator scale. Both of these scales, just for the purposes of convenience, we combined this data, but if you look at them independently for 005 and 006, they do follow the same trends. But in the evaluator scale, which again was a two point improvement at these visits three, four, five, and six, you can see almost an immediate improvement beginning at visit three, as early as visit three and continuing on to visit six with a widening of that gap of the response compared to the vehicle.

The next two slides are just summary slides showing that the following endpoints received statistical significance in the MITT population. You compare 005 on your left and 006 on your right, looking at the live subject assessment in both the two point move and the more commonly-used less stringent one point move, as well as the subject photograph assessment all received -- with the exception of the 006 for the subject assessment in a one point move, all achieved statistical significance.

Let’s look at the same table for the evaluator

assessments in the MITT population, and in this case all visits, all time points achieved statistical significance in these endpoints.

In addition, we did a 12-month follow-up call just to ask patients how they felt about the treatment from their last visit at six months. And, again, this was segregated by cohort 005 and 006. And I believe the N for this was again a 130 to 136 respondents. And looking at the Azfibrocel-T versus vehicle in 005, you can see that at 12 months most people felt that they were the same or better in comparison to their last treatment at six months and this is compared with the vehicle in both. And then 006, again, most people felt that they were the same or better in comparison with the vehicle for 006.

These patients had not received any future cosmetic or any other cosmetic treatments since they were released from the visit six up until this survey.

So briefly, let’s look at some of the subject photos. This is an example. Again with baseline at your left, visit six on your right. Judging each fold independently, the subject was dissatisfied at the

baseline and satisfied after visit six. The evaluator appropriately measured moderately deep at the baseline in terms of depth on the left, and then shallow on the left at six months. And on the right side, it was judged as deep at baseline and much better or shallower on the right. So you can see a clinical improvement here.

I'll just make a distinction. This is the crease that we were targeting. This is overhanging fold, just so as not to be a distractor. And you can see a very nice improvement, especially in the distal end of that crease, and also on the other side.

Another example here. This patient, again a baseline and visit six, the subject was dissatisfied at baseline and satisfied at visit six, and the evaluator live assessments were moderately deep and just perceptible for the left and right sides. And the subject photo and evaluator photographic assessments correlated with that very well.

So in conclusion, 005 and 006 pivotal studies met both the evaluator and subject co-primary endpoints with a very high degree of statistical significance.

Fifty-nine percent of Azfibrocel-T-treated subjects and 26 percent of the vehicles indicated somewhat satisfied, satisfied, or very satisfied with their appearance at visit six by the live subject assessment.

Thank you. I apologize. One more conclusion slide in my haste to introduce Dr. Smith.

With the photographs that were reviewed at visit six, 67 percent of the subjects treated with Azfibrocel-T versus 26 percent of the vehicle indicated that their appearance was better or much better than baseline. Again, this is for the photographic assessments; when they were reviewed at visit six by the evaluators, 58 percent of the patients treated with Azfibrocel-T as better or much better versus 21 percent of the patients treated with the vehicle.

Okay. Thank you again for your time and attention.

I'm going to introduce Dr. Stacy Smith, who will talk about the safety of Azfibrocel-T and safety results from these two pivotal studies.

DR. SMITH: Good morning, everyone. My name's Stacy Smith. I'm a dermatologist from San Diego,

California. My practice is primarily one of clinical research in dermatology.

For the purposes of conflict of interest, I was the investigator and a consultant for Isolagen, now Fibrocell, for the Pivotal Study 006, and also for a study that won't be discussed, an acne scar study. My travel, compensation for my time, and lodging are, of course, covered by Fibrocell today.

Further conflict of interest, as a clinical researcher, I serve as an investigator and consultant for a number of sponsors who also produce and develop therapies in both aesthetic and medical dermatology.

I'm going to take about the next 20 minutes to discuss the safety of the Azfibrocel-T treatment for you. I'm the kind of guy who likes to tell you what I'm going to tell you and tell it to you. Here's the list of what we're going to talk about.

We'll talk about the safety experience in the commercial of the product. We'll go over the Integrated Summary of Safety or ISS Database. We'll tone down a little bit on the pivotal study data 005 and 006 with respect to safety, take a few minutes to

talk about some subpopulations and their safety, and then adverse events and special interest.

Azfibrocel-T is somewhat unique in that we had commercial experience prior to it coming under regulatory scrutiny. So we'll have an interesting amount of data to talk about with respect to that prior to its study under clinical studies.

There's a second bigger database we'll talk about, the safety database, that includes all seven of the studies discussed earlier by Dr. Weiss, and then the pivotal studies 005 and 006.

The largest experience commercially was in the United Kingdom from about 2002 to 2007. Over 7,000 patients were treated. Between 2004 and 2006, the adverse event profile was looked at a little more carefully and the listed events that were reported are here on this slide. A total of 26 events, almost all limited to injection site reactions, very typical for what you might see with any facial injection therapy. These are all self-limited and most of them resolved without any medical intervention whatsoever.

There were three serious adverse events in the

United Kingdom data. Two of them were allergic-type reactions. One was an allergic-type reaction that was felt to be due to latex or lidocaine and was not by the treating physician attributed to the Azfibrocel-T therapy. The second, however, was an angio-edema or anaphylaxis-type reaction that the doctor thought could be due to the therapy.

An interesting point of difference between the manufacturing in the United Kingdom and what is currently being or will be manufactured in Exton in the United States is that there is penicillin in the United Kingdom product and that is no longer found in the product that’s currently being developed.

One interesting serious adverse event was fibrous overgrowth in the United Kingdom. This is an odd case where the patient had had previous eyelid surgery and had eyelid scars. The treating physician thought it would be a benefit to inject this material into these eyelid scars. There was fibrous overgrowth or enlargement of these areas. The areas were removed. There was suture material found in those areas. The treating physician thought that the suture material

might be contributing to the problem, as well. This problem has fully resolved since that time.

The Integrated Summary of Safety Database is the largest database of subject experience. This includes 508 subjects who were treated with the active product and 354 treated with just the vehicle. Almost two-thirds of the patients reported at least one adverse event and a total of 849 adverse events were attributed to the active group.

In the vehicle group, about 50 percent or a 174 subjects had at least one adverse event and that gave us a total of 532 adverse events for the vehicle group.

It’s important to remember that subjects in almost all these studies have the ability to undergo three injection sessions, so every subject has three opportunities to get an adverse event, and in the ISS database, over 90 percent of subjects did have all three of their injection sessions.

With respect to relatedness, of the 849 events seen in the active group, 443 of them were deemed by the investigators to be at least possibly, probably, or

definitely related, hereafter described as related adverse events.

Looking at the vehicle group, there were 207 out of those 532 events that were deemed related by the investigators. Over 90 percent in both groups of these related adverse events were at the injection site. Almost 90 percent were mild in severity and 87 percent of them resolved within just seven days.

With respect to severity, as I said before, over 90 percent were mild. There's a modest number in the moderate category and a total of six events of the severe type.

Here are those six severe adverse events that were felt to be related. One in the vehicle group was an episode of bruising that last just a few days. There were three severe adverse events, pain, erythema and swelling at the injection site that occurred in a single subject, and there was one injection site swelling in one of the very earlier studies, and one injection site ischemia. The swelling lasted five days, the ischemia lasted two days. All of these were fully resolved by the end of the study.

Looking at the common adverse events greater than or equal to 1 percent, these were all injection site reactions and here's the list of these variously-described types of injection site reactions.

Drawing your attention to the most common, erythema, bruising, swelling and the nodules, and if you look directly at the nodules, we see papules, which is a similar category. Erythema and swelling are more common in the active group.

It's thought that the injection of the autologous fibroblasts plus what other materials are in the product induce a modest inflammatory-type reaction that give you this erythema and swelling.

Interestingly, the bruising is actually more common in the vehicle group. And while this may seem perplexing initially, it's not hard to understand as a treating dermatologist the active product has collagen in it, also causes that swelling. Both the active swelling of the tissue and collagen have hemostatic properties, so it's not surprising that we do see less bruising in the active group and more in the vehicle group.

Nodules. There were 20 subjects with nodules and eight with papules in the active group and only a modest number in the vehicle group. We'll look at those in more detail in a little while.

Looking at the less common adverse events, these are injection site reactions that are less than 1 percent. The top three have -- this is events, not subjects now -- have a total of five events. Remember, each subject has a possibility of getting three chances of an adverse event. There's injection site reaction not otherwise specified, dermatitis, and then some induration. The rest of these are fairly banal and very uncommon.

These next slides are non-injection site-related reactions. They're adverse events felt to be related to the therapy. We have five headaches. Again, these are events, not subjects; four episodes of acne, and then a list of some more banal problems, as well.

I would draw your attention to two here, skin hyperpigmentation, two events, we'll talk about in a little more detail, occurred in one subject. And then

for Dr. King, there was one case of a patient who did have a history of alopecia areata that flared during the therapy but was resolved at the end of the study.

There was one case of basal cell carcinoma that was felt to be related. We'll talk about that in a few minutes. That's at the top of the list. And then, of course, the other very uncommon non-injection site-related adverse events.

Looking now at the 005/006 pivotal database in more detail, a review of the eligibility criteria with respect to safety for the study. The subjects couldn't be in the study if they had been treated with an investigational product or procedure in the 30 days prior to their enrollment. They couldn't have had a genetic disorder that involved fibroblasts or collagen, Ehlers-Danlos Syndrome, achondroplasia, et cetera. They couldn't have a history of an autoimmune disorder, such as lupus or polymyositis, and they could not have previously had an organ transplant.

The diagnosis of cancer, unless it was fully treated or in remission, was acceptable for enrollment, except for basal cell carcinoma. We specifically

excluded basal cell carcinoma in that patients who have had a basal cell carcinoma are at increased risk of getting future basal cell carcinomas. We wanted to keep the study fairly clean and unconfounded with additional risk of basal cell carcinoma because we were going to look at that in detail.

Patients could not have an active or chronic skin condition in the area of treatment or the area where they get the biopsy. Obviously, they couldn't be allergic to anything they might be treated with during the study and they couldn't have an active systemic infection.

In the pivotal study database, there were 181 subjects in the active or Azfibrocel-T group, 191 in the vehicle group. Of the active group, about two-thirds or a 113 subjects had at least one adverse event. This gave us a total of 354 adverse events in the active group. Looking at the vehicle group, again about two-thirds, same number of subjects, 113, had at least one adverse event for a total of 391 adverse events in the vehicle group. Again, patients had typically three injection sessions, three chances to

get an adverse event.

Looking at relatedness of the 354 adverse events in the active group, 191 were thought to be related by these definitions by the investigator. In the vehicle group, 169 of 391 were thought to be related. Of the adverse events that were felt to be related, over 95 percent in both groups were injection site reactions.

Looking at serious adverse events, there were 20 serious events in both studies. They were roughly equally distributed between the active and the vehicle groups and none of them were considered related to the therapy.

Okay. A similar list of injection site reactions we saw for the Integrated Summary of Safety, this is just for the pivotal data, again greater than or equal to 1 percent or the common adverse reactions; the same story, erythema, swelling, and bruising. Again, bruising is much more common in the vehicle group than in the active group.

Papules and nodules, a small percentage, again we'll talk about in just a minute, and then the other

usual injection site reactions, again not unexpected in patients undergoing facial injection therapy.

With respect to severity, again more than 90 percent were mild, a few were moderate, and then there were four severe adverse events in this group. Again, there were three in the active group and that was those three that I showed you before in the one subject.

It's important to look not only at what kinds of adverse events you have and what they are but also their duration. Having a modest adverse event that lasts just a couple days is much better than having a small adverse event or mild adverse event that lasts a long time.

Here's a list of the duration of common injection site reactions listed from the early to the late. Bleeding, not surprising, only lasts the first day. The erythema and swelling typically lasts just two to three days and you can see by seven to 14 days most are gone. Pain is common early but not late. Itching is common early but not late, and then bruising, not surprisingly, appears later. Leakage of blood appears in the skin and the bruise appears some

time later but typically resolves in about a week, although we do have some longer-lasting bruising. And then the papules show up a little bit after the injections are conducted.

Looking at those that did last greater than 14 days, here's the list. We had trace redness in an active patient that lasted about three months, mild puffiness in a patient in the active group that lasted 28 days. Two patients in the vehicle group had bruising that lasted around a month. Two bumps, one papule, one pimple, both in the active group lasted two weeks. There was a patient in the active group who had mild thickness of the skin for two months.

We do have one patient with a ridge at the injection site. This is a palpable sort of induration ridge that is not visible. It was continuing at the time of the patient's last evaluation.

There's a patient who has mild upper eyelid swelling. She had upper eyelid swelling at all three of her treatment sessions. She continues to have a bit of mild upper eyelid swelling at the end of the study. One patient in the vehicle group had some numbness, and

then there was the skin hyperpigmentation. That was one subject who had two episodes, each episode lasting about 20 days.

Looking at a couple subpopulations, we looked at three. One is the geriatric population, greater than/equal to 65 years of age. We looked at male subjects. This is primarily a female therapy, so the males are a minority. And as a dermatologist, we're always interested in patients with dark or Fitzpatrick skin types, so we looked at the non-white subjects.

As a note, we're returning back to the ISS database, not the pivotal study database. These are small numbers of subjects, so to collect as many as possible, we're going to go back and look at that ISS or complete database from all seven studies.

This is the geriatric or the greater than 65 years of age group. To orient you, the two columns here are the vehicle group split out by greater or less than 65 years of age and these two columns are the active group. I would draw your attention again to erythema and swelling. They are more common in the active group in greater than 65-year-old patients

compared to the younger group. This tell us that geriatric patients are potentially a little more reactive, a little more able to induce redness and swelling from the treatment, and that difference is seen at greater than in the vehicle group. The rest of the list of adverse events are not specifically different in the younger and older age groups.

Looking at the males in the studies, the same thing, the same orientation, vehicle group on the right, active group on the left. The things of importance or differences are bruising and swelling. It appears that men are less likely to have bruising or swelling compared to women. Perhaps this is due to the thickness of their skin or the way the injection is conducted.

Then, lastly, the non-white population. Two things of importance. We are focusing on the skin hyperpigmentation. Again, one subject with two episodes and no skin hyperpigmentation was seen in the active group. One thing that isn’t highlighted is bruising. You’ll see again more bruising in the vehicle group but more bruising in the white population

than in the non-white population, probably very easily explained by the fact that bruising is very difficult to detect in darker skin types.

Looking at two adverse events of special interest, nodules and papules are similar to nodules in terms of what happened both in the ISS database as well as the pivotal. This is the pivotal data for nodules. There were four nodules in the active group, one in the vehicle group. They were all mild in character and they all resolved within three days.

We are very concerned about nodules. We will talk about tumor genicity in a second. Nodules potentially could represent early tumor formation or some type of abnormal inflammatory reaction, and that was not seen.

Basal cell carcinoma, another adverse event of very special interest. There were two cases of basal cell carcinoma in the pivotal studies. The first occurred in a 59-year-old Hispanic female treated with the active product. The carcinoma occurred on her left shoulder two weeks after her third treatment. The investigator thought, due to its anatomical location,

that it was unrelated to the therapy. She had surgical incision and remains free of disease in the area to this day.

The second subject is a 76-year-old white female, again in the active group. She developed a basal cell carcinoma on the right upper lip, fairly near the treatment area, was detected five months after her last injection. She underwent Mohs micrographic surgery and had the area fully excised. She remains free of disease at this date. She was noted to have a solar keratosis or an acne keratosis on her nose. This tells us she does have a fair amount of photo exposure and probably is at risk for basal cell carcinoma.

Basal cell carcinoma is the most common cancer in humans, has a fairly high incidence rate in the U.S. in the white population. These two basal cell carcinomas, given the duration of the study and the number of subjects, is not inconsistent with the typical U.S. incidence of basal cell carcinoma.

Some last words about tumor genicity. There are two theoretical concerns about tumor genicity. One is the development of basal cell carcinoma potentially

from the donor area or the biopsy area, if you will. The biopsy area is the retroregular skin. It's chosen because it's easily hidden and is not photo-exposed skin. The likelihood of having a basal cell carcinoma in that area is low. So we feel that the chance of transferring a basal cell carcinoma cell to the culture and somehow transferring that to the patient is low.

The second theoretical concern is that these fibroblasts that are grown autologously will somehow be tumor genic and make tumors, and that's simply not seen or reported typically. The cells here undergo a few number of passages. They are not exposed to any genetic manipulation or transforming agents. Additionally, the release specifications for it include morphology examination to ensure that there are not any abnormal cells.

To sum up all the safety, there were common adverse events seen with these injections, typically redness, swelling, bruising, bleeding. The overwhelming majority are mild and they're very short-lived. There are some rare adverse events, again mostly in the injection site areas, lumps, bumps,

papules, pain, other sort of non-specific reactions and itching. They're also very self-limited and resolve promptly.

We saw no unresolved nodules, papules, anything that could tell us that there may be some tumor brewing. There were two basal cell carcinomas in the study and we feel those are consistent with the normal incidence of basal cell carcinoma in the U.S. population.

With that, I'd like to invite Dr. Weiss back up to give us his clinical experience and the market context for Azfibrocel-T.

DR. WEISS: I won't introduce myself again because you already know me.

Basically what I'm trying to do with this is to give some perspective and understanding as to how this would help me in my practice as it currently is comprised.

So I'm going to briefly touch on the position in the aesthetics market, the duration of effect with my experience from the patients that I treated in 2003, a little more detail about the clinician experience,

and then touch very, very briefly on the future.

This is data from ASDS, which they publish frequently. We know that there were 10 million surgical and non-surgical cosmetic procedures performed in the U.S. in 2008. That might change in the recession in 2009, but surgical procedures accounted for 17 percent, non-surgical procedures making up 83 percent of the total. And they have increased 162 percent since 1997 because there have been a lot more options available, and the non-surgical procedures have increased by over 233 percent.

This data from the American Society for Dermatologic Surgery indicates that the treatments that we're doing include all of these for treatment of photo-aged skin. And certainly the number of soft tissue fillers has exponentially increased, although so far only a relatively small amount of the market that would potentially benefit from this has actually gone ahead and done fillers.

Of course, botulinum toxin, we do a lot of fractional laser resurfacing, and sort of botulinum toxin is probably number one, fillers two, fractional

number three. And we know about the current treatment of nasolabial fold wrinkles. We have the sort of Legacy collagen product prior to the hyaluronic acid products. Those are injected high in the papillary dermis, so then you have the cross-linked hyaluronic acids which are injected in the very deep dermis or in many cases when more highly cross-linked are injected at the interface of the dermis and subcue tissue. Botulinum toxins, indication frown lines, off-label indication crow's feet, but really cannot be used for improvement of the nasolabial folds or much in the lower half of the face.

So the market position for this product would be a novel cell-based product for treating nasolabial fold wrinkles via a biologic mechanism of action. It's a new class of treatment. Its clinical effects will provide a treatment option not currently available with any other aesthetic product. And I know when I was enrolling patients in the 002 and 003 studies, there were many patients that embraced this concept of getting their own cells.

There are many people who I see every day who

are vehemently opposed obviously to getting a toxin injected into their skin, nor do they want a hyaluronic acid that's been made in a lab that's bacterially produced. You know, they hear something like that and they definitely will not participate with that. It's like what else can you do.

We know that this will have a gradual onset effect, similar to another product that was just cleared, Sculptra, and there is a market for a gradual change. And we know that there's at least six months duration of effect. And I know from my experience, following patients since 2003 and 2004, that it's potentially long-lasting.

I just wanted to share. I was able to -- because we have a photographic system where patients get a photograph before getting fractional resurfacing or other procedures, I've been able to see and document some people over a long period of time. This is someone who had six months post-treatment in the 002 study with a nice improvement, and then here she is six years post-treatment with maintenance of improvement. So if you look at the end of the study and then follow

up six years later, just before she's getting fractional, you can see in the areas where we didn't inject, there's certainly more progression. But I felt, looking at a whole series of photographs, I can only show you one at different rotation, that certainly still it was better than baseline in 2003.

Here is a similar patient. This is where she's six months post-treatment and then here she is three years post-treatment about to get fractional ablative resurfacing. And we can see, if we go back to six months post-treatment, and she agreed, too, that really there has been very long-term improvement. You can see the continuation of her photo-aging in the meantime.

This was a two point improvement. This is from the 003-B arm looking at the patients, examining them, having them back to the office at 12 months, that it appeared not statistically significant but that the trend for this to be long-lasting is certainly there, and with a similar percentage still maintaining that two point improvement.

So what do we think about the future? Well,

we're presently conducting acne trials. I have followed some of the patients that we injected in the 002 study back in 2003. This is the problem with photography where the flash is dead-on that you can't see a two to three millimeter improvement in the scarring. But this is a patient who actually had tears of joy when we were seeing her in follow-up, and I think this is going to turn out -- my prediction would be an important therapeutic option for acne scars since we can do things with fractional lasers but not like this.

There's been some evidence in the U.K. about restrictive burn scars. There's been some talk of full face treatment to maintain a more youthful smooth appearance, but that we can do with other things, and a whole host of aesthetic and therapeutic indications, such as gingival retraction, which many people, including myself, experience after the age of 50.

So in summary, Azfibrocel-T is a novel autologous cellular product for treatment of nasolabial fold wrinkles. It provides wrinkle correction through a biologic mechanism of action. The biologic effect of

Azfibrocel-T is gradual in onset, but the evidence is there, and I firmly believe that it is potentially long-lasting.

So we now go to our final presentation, Jeanne Novak, to discuss the post-approval safety assurance and concluding remarks.

DR. NOVAK: Again, I'm Jeanne Novak, the authorized representative for Fibrocell.

Again, we'd like to thank the committee, the FDA, and the public who are in attendance today, to give us this opportunity to present both data and opinion about the utility of Azfibrocel-T.

So just in summary, I just want to touch on a couple of interesting points that one would bring to the forefront with regards to how does one bring an autologous product, a live viable cell product, to the market. And given the fact it's a patient-specific product, what are some of the considerations one should have and what are we planning to do to ensure product accountability, appropriate injector and physician training, as well as safety follow-up post-approval.

The current plan is that Fibrocell will

establish centers of excellence and these centers of excellence will be established for both training as well as centers for establishing safety and oversight of the commercialization of Azfibrocel-T.

For example, the centers of excellence, the intention is to include investigators who have had experience previously using Azfibrocel-T in studies that have been done under IND. These investigators, having not only been trained in injection technique but also the appropriate follow-up and product disposition, will be pivotal in training any new physicians we bring onboard as physician prescribers.

The centers of excellence, of course, with our physicians in the clinic, will assist us with some of our training activities and all of the centers of excellence physicians will be refreshed and retrained in the areas of biopsy collection, label and shipment, labeling and shipment of the biopsy, the Azfibrocel-T injection technique, certainly product accountability again for patient specificity, and the reporting of adverse events and any product-related issues.

In addition, Fibrocell is working to establish

what we call a clinical support center. The goal here is to have one centralized location that will consolidate and review data for a number of various purposes. Again, being an autologous product, not only is it important to track biopsy to injection, it's also important to manage the manufacturing schedule. A scenario might be a patient comes in, would like to receive the Azfibrocel-T, however if patient biopsies were just randomly collected and sent to the facility, the manufacturing capacity is such that those biopsies may not be accepted.

So in order to manage the logistics around the receipt of the biopsy and the scheduling of patients, this clinical support center would provide the coordination of both the patient and production schedule. So the centers of excellence and our prescribing physicians would be in direct communication with the center in order to establish schedules for biopsy and then subsequent administration of the product after the 90-day production period.

Again, the centers of excellence, with our physicians who have currently extensive experience with

the product and the technique, will be training other physicians. They will be pivotal in establishing for us the appropriate safety parameters that should be monitored and collected in the post-approval scenario, and also the clinical support center will collect customer complaints directly through an interface to both the patient as well as the physician.

So turning to product accountability, over the several hundred lots of IT that have been manufactured, either previously in the Houston facility -- and let me rephrase, IT also refers to Azfibrocel-T, that was the original designator -- of over hundreds of those lots that have been manufactured in either Houston or Exton, there have been no incidences where the product has ever been sent to the wrong patient or clinic. That's been established through computerized systems of scheduling during the IND phase and an extension of that, more extensive in fact, computer database management system is to be established that will also assist with the labeling and tracking.

One of the goals then is with the labeling system, it's important first that specific patient

labeling occurs at the time of biopsy. This is key to establishing good accountability and again to establish a database that would also support safety reporting.

Three independent and unique identifiers are planned to be used for the tracking purposes: initials, birth date, and a lot identifier that's unique to that patient and product. The unique lot identifier will be the number that's used throughout the manufacturing process.

One of the reasons, of course, to have both patient information, again date of birth as well as initials, is so that the verification process comes full circle. For example, once the Azfibrocel-T product is actually sent back to the clinic in vials ready for injection, the patient-specific information as well as the unique identifier that was given to this product will be verified by both the clinician and the patient in order to establish assurance and prior to that injection.

With regards to the safety data collection, we feel a pharmacovigilance program is appropriate for this launch of this product and the pharmacovigilance

program in our case actually is going to be fairly robust just by the nature of the product itself.

Being autologous and being that we are registering these patients as they come in at the time of biopsy, we have a unique opportunity to track on a case by case basis all adverse events or any unusual occurrences that we might see upon commercialization. So at the time of biopsy, the patient information will be collected and entered into a registry. Again, this will occur at the clinical support center.

The prospective safety data will also be collected upon the initial launch of this product and that's specifically to collect in a very defined fashion serious or unexpected adverse events. We also want to understand product utilization and demographics as well as any particular product administration and errors or errors in shipment or receipt of the product. We feel this is important again for an appropriate launch of a product as unique as Azfibrocel-T.

Last but not least, we will also have a data system for spontaneous safety reporting. So in addition to a prospective defined pharmacovigilance

program, we will establish a spontaneous safety reporting system.

So in summary, Azfibrocel-T has been demonstrated to be safe and that’s been established in both prior commercial use and in seven INDs that have been used to support the Integrated Summary of Safety. Expected adverse events with Azfibrocel-T are mostly mild, primarily occur at the injection site, and resolve in less than a week.

With regards to the efficacy for nasolabial fold wrinkles, the clinical efficacy, of course, has been demonstrated in controlled studies 005 and 006. Interestingly enough, statistical significance for the treatment effect of Azfibrocel-T over vehicle was seen even when assessed by subjects as early as 003-A and B studies.

Statistical superiority of Azfibrocel-T to vehicle was observed as soon as 10 weeks after the first treatment in our 005 and 006 studies, and we believe, although the current label indication is for up to six months of use -- or up to six months in duration, I should say, Azfibrocel-T does have the

potential for the duration beyond six months and with that, I can tell you Fibrocell is very interested in conducting further IND studies to establish both the duration effect as well as repeat treatment use and safety.

Thank you again, and I'd like to turn this back to the committee chair for any questions to the sponsor.

DR. GERSON: Thank you. We will now begin the question period. I want to compliment the sponsor on keeping exactly on time and giving us an extra minute or two and for their informative and comprehensive review.

We will first start with a comment from Dr. Witten.

DR. WITTEN: Thank you. I just want to comment that although the sponsor's provided data and opinion about mechanism of action and duration of effectiveness, that there's no data that speaks to biological mechanism on this product that I'm aware of from their presentation in animal or human studies and also no data from studies designed to evaluate longer

than six-month effectiveness in the clinical studies.

So when we have the afternoon discussion, we will ask the advisory committee to focus on a discussion of actual data informed, of course, by their understanding of the literature and the science.

Thanks.

DR. GERSON: Thank you. So I would now like to open up the discussion. We'll start with Dr. Allen.

DR. ALLEN: I'd like to actually compliment the sponsor on a really very thorough presentation. So I've got really a question, I guess, relating to some of the release criteria.

So I didn't hear an enormous amount -- obviously it's difficult to include everything. But I guess I'd like to get a sense of really one thing, which would be we saw a number of the things that are measured in terms of viability and obviously sterility, et cetera, but in terms of there was mention of collagen, and I guess I'd like to know what the criteria are for collagen, whether it's simply total amount of collagen or types of collagen or some ratio.

I guess specifically, out of all of the lots that were prepared, how many lots failed?

DR. RAO: Can I add a couple of questions so they can answer at the same time?

So lot failure, you know, it's also the residual contaminants that are present in the lot, including DMSO and SITA components that were used. And you mentioned something briefly about penicillin in the early manufacturing process, and maybe they can add some more detail on all of the sort of standard manufacturing process, as well.

DR. NOVAK: I'm not sure if that mike's working, so I'll take the question from here. And I'll ask Mr. John Maslowski to join me for specific numbers.

With regards to the release testing and specifications, the tests that are done for collagen, it is a collagen content assay. As far as the production and the detection of collagen, all lots that have been tested to date, which is a subset actually of approximately 50 lots, have all demonstrated new synthesis of collagen.

With regards to specifications, we weren't

going to discuss that specifically here at the meeting, but the requirement going forward will be that we do have and have established a threshold for the amount of collagen we expect to see upon harvest of these cells, in addition again to the viability criteria.

Are there more specifics that you'd like to ask about that issue?

DR. ALLEN: I guess my interest is in moving forward and having large numbers of things, it would be of interest, and these are potential measures of potency. And one of the things that would be tremendously interesting as you get numbers would be if you can demonstrate -- for example, there's a couple of things.

So, for example, you demonstrated, I think, a two-fold difference between the fastest passaging cells and the slowest. So to me, it would be interesting to see if there's a relationship between the proliferative capacity of cells and the result you get. Similarly, it would be interesting, is there a difference in Type I to Type III ratios in terms of the response, the amount that you get?

So I think it's more about the context of are provisions in place to prospectively look at these things, to use these as surrogates of potency?

DR. NOVAK: Yes. Actually, thank you for that additional part of that question.

Again, the dataset going forward at this point is fairly limited, but in fact that's exactly what we plan on doing, to look more discretely at the ratios of collagen produced, other attributes of the product itself, and this is through discussions with the FDA reviewers, again for the same sort of rationale, with the rationale behind it; can we eventually link the activity of any of these particular characteristics and culture with potential characteristics and prediction of potency in the clinic, as well. I'll stop there.

John, did you want to comment on the number of lots, success and failure?

DR. WEISS: Right. The lot failure was generally around events of OS and of these types. What we saw was variability in the ability of certain lots to actually achieve harvest. So we're talking more of like a cell proliferation issue.

There were 24 lots that were identified that we had some of these issues with. However, going forward with our later clinical trials, and we worked with the FDA on actually creating more of a standardized process based on the results of 005 and 6, which we actually allowed the ability to passage a 1 to 2 ratio from simply from a single flask to, say, 2. In order to address any of the -- kind of the broader variability that we didn't see, like some lots potentially that get to the harvest stage that quite didn't have enough cells for the full treatment, well, they just needed a simple shallow passage.

So we actually now in our CMC have this ability for this short split if we don't achieve that, which help this cell failure rate that I described.

DR. GERSON: Dr. Taylor.

DR. TAYLOR: I have a couple of questions regarding the release criteria and then a few about the patient population.

The release criteria, so do you maintain cells from each biopsy? I noted that no karyotyping analysis has been done. In the patients where basal cell

carcinoma occurred, was there any karyotyping done retrospectively?

DR. MASLOWSKI: There was no karyotyping done on patients.

DR. TAYLOR: And are cells maintained and stored for the long term?

DR. MASLOWSKI: Yes, they're stored in vapor phase LN2 onsite in Exton.

DR. TAYLOR: So even in the cell samples where there was a harvest failure, you do have cells stored for safety analysis retrospectively?

DR. MASLOWSKI: Yes, we maintain cells from the lots.

DR. TAYLOR: And my understanding is you grow the biopsies. You take three biopsies. You grow the biopsies for approximately 90 days. The cells are stored frozen and then thawed in three separate samples for mailing to the treatment site at the time of treatment.

DR. MASLOWSKI: On three separate occasions because the injections are over five-week periods.

DR. TAYLOR: Right. And have you compared the

three sets of samples in any of these patient populations to -- are they identical at the time of thawing and shipment?

DR. MASLOWSKI: We see very similar release criteria from injection one to two to three. We haven't seen any degradation of cell count for shipment, especially viability has been very consistent.

DR. TAYLOR: What about potency?

DR. MASLOWSKI: Potency was also quite consistent, and we didn't see any statistical difference from, say, injection one to injection three during the analysis we performed.

DR. TAYLOR: And you said the cells are greater than 98 percent fibroblasts. By what criteria?

DR. MASLOWSKI: We use a potency assay at what is called the drug substance, stage which is where the cryopreservation stage occurs, using flow cytometry method that has an antibody to a cell surface protein that is specific to fibroblasts, and then we use an impurity cell surface protein that is -- well, a transmembrane protein that is specific to

keratinocytes, which we identify as the potential impurity in our product because it's one of the competing cell types in the epidermis-dermis sample. And the comparison of this gives us this ratio to 98 percent or greater.

DR. TAYLOR: Having spent 20 years looking for a marker that's specific to fibroblasts, I would be concerned about that.

DR. MASLOWSKI: No, it's not cell-specific, but they're unrelated. So, for instance, the marker is specific -- is expressed in fibroblasts but not keratinocytes, and the impurity is expressed in keratinocytes at a high ratio but not fibroblasts.

So after the culture has been purified from multiple passages through the process, when we get to the end, we've identified those two as being the most possible cell types to be present in the sample. That's why we developed the marker system in that way.

DR. GERSON: Dr. Taylor, I'm going to move on. We've got eight other questioners.

DR. TAYLOR: Just one other question about --

DR. GERSON: We're going to come back.

Dr. Woo.

DR. WOO: Thank you. I have a couple questions on the efficacy side of the equation. So I'm not a dermatologist and so I'm sure the dermatology colleagues can comment on the validity of all these investigators' evaluations of the outcome.

So it kind of struck me that the efficacy endpoints is really quite subjective. We're relying on individuals' impression of what the effect is, whether it's two points or three points or one point.

So I was wondering in this age of computer-assisted topography, we can map the surface of the moon, why is it that we cannot come up with instrument-based objective assessments of the clinical outcome?

DR. NOVAK: Thank you for the question. I think first I want to address the scales, and I think my colleagues have done that well, because, in fact, in order to achieve two pivotal studies using these scales and the two point move, especially on the Lemperle scale, it required some training. And that's why, for example, you would notice that we did not achieve statistical significance for the evaluator assessment

in the early, the two original sets of pivotal studies. And we actually believe it is because of the scale, that the utility of that scale and the application to clinical trials is a little bit more challenging. And, in fact, Fibrocell historically has gone back and trained --

DR. WOO: Excuse me. That's not my question. My question is has there been any attempt to develop an instrument-based objective measurement of outcome?

DR. NOVAK: At Fibrocell, no, there has not, and I would like to ask one of my dermatologist colleagues what you would -- if no is enough of an answer, we'll stop there. But no, we have not. We've used the visual assessment --

DR. WOO: Then the question is why not?

DR. NOVAK: All right. Very good. And again, I think from a clinical perspective, this becomes apparent.

DR. WEISS: Obviously, this is an unmet need and we have worked on numerous systems. One took an image and did optical topography. The problem with that was the slightest move in the positioning of the

patient, you'd have these fancy maps and numbers, but you could actually take the same patient and try to reproduce it two minutes later before any treatment, and you would get slightly different results. And so, the moon, I know it's moving but it's probably not moving as much as an investigator and the patient.

DR. GERSON: Thank you. So at the moment, we don't have an established method, is that fair?

DR. WEISS: There's a 3-D vectra system, but it's not yet been validated for studies and it might be in a year or two that that's available.

DR. GERSON: Dr. Kwak.

DR. KWAK: I just have a couple of technical questions.

The first is on Dr. Novak's presentation, there was some variability in the number of cells that are contained in each vial and I don't quite understand the reason for the variability.

The second is what is the physical appearance of the material that's injected, and is this really legitimate to do a double-blind study?

DR. NOVAK: With regards to the variability,

that's actually an established range that is targeted for the production of the final drug product that's to be injected and that range, is between 10 and 20 million cells per ml. And again, the injection is at .1 milliliters per centimeter.

It's interesting you would ask because we've had again discussions with our FDA colleagues and are looking to tighten that specification as we move forward. That's not currently in the plan for the initial launch, but again the hope is that we can begin to target our manufacturing process with a tighter range.

I'm sorry, Dr. Kwak. What was the second question?

DR. KWAK: The second question was, were the investigators really blinded? What was the physical appearance of the vehicle versus the product?

DR. NOVAK: Well, as one would imagine, it is a cell suspension and it is delivered to the clinic in, if you will, a cryovial, which you know is opaque. And I would like Dr. Smith to come and join me because in the actual preparation, there were a couple of efforts

made, one to have somebody else prepare the actual syringe containing the material, for example a study nurse, et cetera. But with regards to the actual blinding, we actually did an assessment to see whether or not either the injector or the patient might have felt they were unblinded during the course of the study. And I'll let Dr. Smith address that more specifically.

DR. KWAK: I guess my concern is the syringes are clear, so whoever's doing the injection can theoretically see the difference.

DR. SMITH: It's important to understand the study design. There were injecting physicians and evaluating physicians, and an injecting physician was never an evaluating physician for a given subject, so that the evaluation was done by someone who never saw the injection process.

This was not a bilateral design. The patients got the same thing on both sides. Patients really aren't that facile with particular therapies. They don't know if it looks red or blue or whatever in the syringe. Whatever they're getting is whatever they're

getting.

It’s clear that there are some modest differences. It’s a little bit cloudy, opaque. In some ways I could probably tell what I was injecting, but again it’s about the evaluator blindedness that makes the difference. Patients were also blindfolded during the injections.

DR. GERSON: Dr. Newburger.

DR. NEWBURGER: Thank you.

To that point, Dr. Smith, you’re certain that there would be no bias of the person who’s injecting knowing that they’re using an active -- I mean anyone who’s worked in cell culture can really tell the difference with a cell suspension. So might there be some type of difference in terms of the actual injection?

Another question for you, sir, is you mentioned that there was some collagen present in the active product, is that correct?

DR. SMITH: Yes, second one first. My understanding, there is collagen as part of the release spec for the product. So there is some collagen that

you inject in that cell suspension.

DR. NEWBURGER: Could you comment on that then?

DR. NOVAK: Yes. Just as an extension of that, when we talk about collagen, we know the cells themselves are capable of collagen synthesis. The collagen that would be associated with this product is from the cells themselves. There's no additional collagen or any other excipient put in the cell suspension that would contain collagen.

DR. NEWBURGER: The reason why I'm asking of that is there are some reports with other types of non-permanent fillers showing that if you stretch the fibroblasts over time, you're going to have increased production of collagen.

So I'm wondering, do you have any data to show that the benefit is not due to in fact other things that are present besides the fibroblasts?

I also would like to know is there any bovine serum albumin present in the product? I'd also like to -- should I give you all my questions now and you can divide them up?

I'd also like to know, the telephone calls that were given in the 12-month follow-up, in our packet we were told there were two questions which were relating to medical issues.

Was there any specific question directed toward do you have firmness or do you have any developments of lumps or bumps at this time as opposed to those who would specifically volunteer that or the several individuals who had reported that?

Last of all, I was struck by a big difference in the efficacy evaluation on the part of the observers between the two study sites. Do you think that this is a difference in technique or do you think there's a more upbeat or healthier population in the center that got the better results, or have you been able to find any difference in the fibroblast growth patterns in general between the two sites?

DR. SMITH: Where to start? You asked initially about as a person who does a lot of cell culture in theory, you could tell culture cell suspension versus a suspension that has no cells. And in theory or in practice, potentially there's an

ability to tell the difference. It is a thin suspension. It is injected very superficially.

I'm not a cell culture expert and most of the investigators were chosen not because they're cell culture experts but because they're experts with aesthetic therapies and injections. So they may not actually have a lot of experience with what that product looks like or not.

That being said, yes, there is a possibility they could be unblinded by the difference in appearance between an active treatment and a vehicle treatment, and that's exactly why there was a blinded evaluator in all those cases. And in good clinical research, for study execution, you're asked to be very bland and not discuss the therapy with the patient, and we take that very seriously. We don't, oh, this is working really great kind of stuff, the comments you might make to the patient. And again, the patient was blinded.

Next one, bovine serum albumin.

DR. NOVAK: With regard to bovine serum albumin, again all components that would have been part of the culture process as well as any components from

cryopreservation of the drug substance are washed out through extensive washing. And again, the cells are resuspended in a rich media minus any other protein additions or BSA.

DR. NEWBURGER: Are we allowed to bring up one of the documents that we received in the additional packet regarding the British experience?

DR. GERSON: Could we get a response first to your question about the site differences in the studies?

DR. SMITH: The site differences? There were differences when individual sites are analyzed and when the 005 versus the 006 results are analyzed.

It’s felt that a lot of that is due to interpretation or implementation of the scale. It’s a very, actually, harsh rating criteria. A two point move on the Lemperle scale is a very high threshold, and some evaluators will take that more seriously and be a little more assiduous in their application of that scale.

To the commenter or the advisory panel member who talked about scales and wanting objective measures,

welcome to the world of dermatology. This is what we have for these tools and they are somewhat variable.

DR. NOVAK: I think I can address the latter part of that, as well.

We looked at the three sites where the response rate was less and we did not see any differences in the product release specifications. We could not determine that there were any differences in the injection technique proper. There was no reason to believe from at least our initial evaluation that there was anything with, again, product or injection. We do again believe it was scale.

We haven’t queried -- we did do some demographics with regards to the age of the populations; again, didn’t see anything there. Nothing specific that would really point to anything other than the scale, and I think the last part to that is if one looks at the subject evaluations between 005 and 6, in fact the subject evaluations are probably more consistent. So we do believe it was the use of that evaluator scale.

DR. NEWBURGER: Excuse me. But I see between

both of those centers, yet the response in the vehicle alone was the same. So if there really is a difference in scale interpretation, I would have expected to see it there, too. I think they're like 7 percent, something like that, but they were identical. So that's an issue.

When I asked to look at the photographs of some of the individuals which were, I believe, individuals selected at random, I was also -- recognizing that this is a secondary endpoint, I was struck by the fact that there's different lighting, different angles, with the before, with the baseline photographs, and the end of assessment photographs at six months. And I also was struck by the apparent enthusiasm of one particular evaluator, I think, because in photos where I really -- and I see these a lot, I mean, because of other work. I couldn't see a difference in a number of them where a particular evaluator said, yes, there's a two point change.

So I have some concerns about how individuals are looking at the scale.

DR. NOVAK: Thank you. We appreciate that.

And, again, just to comment, we don't believe that the photography can completely provide the assessment to the depth and the accuracy of live assessment. That's why it was chosen and agreed upon with the agency, and we certainly appreciate that. It's not always the concordance one would hope.

DR. GERSON: Can we move on?

Dr. Burke.

DR. BURKE: I have several questions. The first is that we know this product has been used in the United States in the '90s, and then in the U.K., and then in Australia and New Zealand. And I wondered if -- I have several questions -- but why, the reasons exactly why it was discontinued at all of those times?

The second is that because it was used then, theoretically you could have very long-term studies by reviewing some of those patients. And we dermatologists and plastic surgeons know that with the non-biologics, the side effects are over 10 years later sometimes. So I wondered if any attempt has been made to just check on those patients.

I've two more questions that are different.

One is that when bovine collagen was first on the market, we saw with the Zyplast that there was sometimes very serious grabellar ischemia, and so it was recommended to use the lesser concentrated, lesser cross-linked product in that area.

In this case, you're injecting cells, which are larger than molecules of collagen, and you're injecting a mixture of collagen. We don't quite understand how much is Collagen Type I and Collagen Type III, which is more finely fibrillar and less apt to block an artery.

So it is impressive that there are no long-term very serious adverse effects in the data presented, but I just want to caution -- and I was also surprised that you could inject this through a 29- or 30-gauge needle. But I just wanted to point out the possibility of ischemia and if you've actually looked at the size of everything being injected, particularly the collagen.

My last question is that we know that the injection is 98 percent fibroblasts and we're kind of presuming the other 2 percent of cells are

keratinocytes. But I just wanted to point out in keloid scars, it's been found that there are an increased number, an increased activity of mass cells. And particularly in non-white populations that are more apt to keloid, I wonder if you've ever looked particularly in that subset of group or perhaps this should be done in the future, just look for mass cells, just have some marker, because even 1 percent mass cells could lead to a keloid or nodule.

DR. NOVAK: Again, thank you for the comments and questions. We haven't yet looked at mass cells, but that seems like quite a nice study to do, and I think if we have the opportunity in expanding the population demographics, it's something we would certainly want to consider.

Going backwards, with regards to the specifications for purity, the 98 percent is a specification. We believe that in fact the actual result for purity is higher. Again, the 98 percent is based on a dual marker ratio for keratinocytes and fibroblasts.

When we look at the validation of those

assays, there are sensitivity issues around the assays. We don't always get a 100 percent or 98 percent, whatever, in the actual assay detection itself. So there's always some percentage of the population that you're never 100 percent sure that you're 100 percent pure.

So we set that specification based on the two markers we have and the ratio of those markers, and, again, the criteria is that you must be 98 percent or greater. And, in fact, many of the lots, as we deem them from this dual assay, in fact have a much higher purity than just 98 percent, upwards of 99 and 99.5, based on the sensitivity of our assays and the ratios.

With regards to the Zyplast, my clinical colleagues have in fact discussed this issue. I don't know if there's additional clinical comments you'd like to make about the ischemia associated with the early Zyplast, other than at this point again we have single cell suspensions and those single cell suspensions, again, we don't believe -- for the minor events of ischemia that we did see, they resolved, and we don't believe that -- we don't have any more

characterization, other than, again, with regards to size, the average size of a fibroblast in suspension. And I'll mention the U.K. and U.S. briefly and then turn this over to Dr. Weiss.

The experience in the U.K., again, was a commercial experience. It was discontinued for business strategic reasons. The manufacturing was done in the U.K. and it was again a business operation that was discontinued a few years back, and the decision was primarily Isolagen at the time, which is Fibrocell, was intending to focus on the U.S. market.

The discontinuation of U.S. commercial distribution was a direct result and a change in the regulations regarding cell products and regulation by the FDA.

DR. GERSON: Could we just restrict the ischemia conversation to this product?

DR. WEISS: I just want to say when you have a lot of exposed collagen fibrils, it's a very potent stimulator of the clotting mechanism. And I had the same trepidation back in 2004, injecting the glabella. We did 15 patients, but I didn't see anything like I

did with collagen. And, obviously, I don't inject any collagen products in the glabella, and even hyaluronic acid products, I do with great trepidation. But I think it's more of the amount of exposed collagen rather than a pressure phenomenon or particle phenomenon.

DR. GERSON: Dr. Drake.

DR. DRAKE: Mr. Chairman, thank you. I find myself in the unfortunate position of asking a question in the middle of people's break. So I'm going to limit it to just one question that I think is particularly interesting.

You didn't mention any biopsies, post-treatment biopsies or histology, and it seems to me this would be a very important factor in determining what happens after injection and what's actually going on, because then you could look at your markers and et cetera. And maybe you have done them and just didn't mention it, but if you have not done them, I'd like to ask, first, if you've done that, I'd like some data or some results, and if you haven't done them, I'd like to know why not because I think that's an essential

ingredient into this type of study.

DR. NOVAK: Thank you for the question. No, we've not done biopsies of these patients, and the primary reason is because the treatment area is facial, facial aesthetics, and we feel it would be counter-indicated for, again, observations.

Now, we can do and have considered doing biopsies and actually doing studies in areas that would be less obvious, but the reasons these areas have not been biopsied is because the injection area and treatment is on the face.

DR. DRAKE: I have a follow-up to that. I think that's -- with all due respect, I understand your concerns, but I don't think that's a legitimate reason not to do them.

There's always a subset of patients that you can get special volunteers, particularly in the elderly populations, particularly in men, there's always a group of patients who will be willing to do that with proper explanation. And so I don't think using aesthetic appearance for a post-biopsy is a legitimate reason for not doing these studies.

DR. NOVAK: Again, thank you. My only other comment is we have the opportunity in other indications using this product. For example, such in the restrictive burn scars that we intend to treat under IND, in this particular population we've already considered and looked at informed consent to evaluate biopsies post-treatment in these individuals because, again, we were more concerned about the aesthetic piece. But from the scientific mechanism point of view, yes, I do agree. I think we can find populations that would agree.

DR. GERSON: We're going to move on to Dr. Chappell.

DR. CHAPPELL: Yes. I'll also keep my question short.

The committee is provided with written comments, and some of these have raised questions in my mind which I'm afraid I can't ask because the comments are labeled confidential. So first I'd ask Gail Dapolito to what extent I can quote them or even refer to them.

MS. DAPOLITO: There was public comment

provided per the Federal Register Notice. There is a copy of the public comment publicly available at the registration desk in the viewing binder. The committee has copies of the comments and the sponsor has copies of the publicly-releasable version of the comments.

We would ask the committee not to divulge specific names and any personal identification confidential information.

DR. CHAPPELL: Okay. So I can't quote from them without the names.

So there seems to be a furor in the U.K. and I certainly realize that anecdotes are just anecdotes. A woman who was treated with what was then Isolagen therapy claims participation in a class action lawsuit with side effects including local paralysis and joint pain and swelling. She wrote a letter to a prominent medical professional with a prominent position, and that medical professional seems to agree with her. And so I just wanted to give you a chance to respond, although I think I have to be vague here in my quotes and references to what went on in the United Kingdom and ask how relevant it was here to the present

situation.

DR. NOVAK: Sure. Again, thanks for the question.

Declan, I'd appreciate it if you can assist me with a response since you have the history with the U.K. operations and the particular patient issues.

With regards to -- well, I'll let Mr. Daley address it.

MR. DALY: I heard reference to class action lawsuits. The company, we have no class action lawsuits. There is in our public filings very clear reference to a legal letter we've received complaining about false advertisement, so that's all on the public record and our 10-Q, so I can get that for people. But we're not being sued. So I'm confused. So we can certainly show you that public reference. It's a public document, our 10-Q.

DR. CHAPPELL: They quoted the case and the case number. Should I repeat it?

MR. DALY: It's not a case number against our company.

DR. CHAPPELL: Well, against Isolagen

Securities and Derivatives.

MR. DALY: Isolagen, Inc. is the holding company.

DR. CHAPPELL: Right.

MR. DALY: But as far as I'm aware, we have no class action lawsuits.

DR. CHAPPELL: This is quoted. I cannot say whether it's accurate. Should I --

DR. GERSON: I think you've queried, they've responded. We have it in the public record.

I'm delighted with the questions. You guys are doing a great job, but we do need to move on through the day. So I'm going to ask for quick queries and responses just so we can spend no more than five more minutes.

Dr. Dubinett will go first.

DR. DUBINETT: Very quickly. I have a question on the centers of excellence and so if I'm a physician outside of the centers of excellence, will I be able to participate? It somewhat goes to Dr. Newburger's question because I think it wasn't in my mind exactly answered.

If in fact I'm outside the centers of excellence, will my training be as stringent as the investigators, less stringent, more stringent, and complete, compared to the investigators that participated?

The second question is in terms of the morphologic examination of the cells before release, what are the qualifications and education of the person doing that assessment?

And finally, I think Dr. Burke mentioned something about the 29-gauge needle. I'm really wondering if an assessment has been made about the impact of the cells through that gauge needle.

DR. NOVAK: Yes. I'll make these brief. With regards to the training and the centers of excellence, again initially the soft launch of this product will occur already at sites with investigators who have been trained.

Can other physicians participate? Yes, and the training will be as robust. Let me remind you that, in general, the feedback from the clinic is the injection training itself is quite adequate in the

course of a couple of hours to be quite proficient at targeting the papillary dermis.

So the training program, yes, will be extended post-launch for other physicians who are interested. We'll use the centers of excellence again as a location for training as needed.

With regards to morphology, morphology assessments are done of the cells while they're still adherent at harvest in the flasks. That's for drug substance. That morphological examination is against a standard and, yes, individuals in the GMP facility are trained in the assessment of morphology, again specifically looking for fibroblastic morphology.

With regards to the 29-gauge needle, we have looked at other gauge needles. We have also in fact done a study to deliver cells through that 29-gauge needle and assess them for the characteristics of viability as well as cell count, again to address issues potentially of shearing, clumping, decrease in viability, et cetera, and those studies have demonstrated that a 29-gauge needle does not impact the product with regards to viability or any other

characteristics from those studies.

DR. GERSON: Dr. Snyder.

DR. SNYDER: My questions, I'll make them very brief, and they may be actually answered after the next set of presentations concerning mechanism.

One, I was just wondering, do you know how long the injected cells survive after the injection, whether they migrate and the extent of the new collagen?

My second question is given the mechanism that you do think that these are cells that respond to injury in fact through the injection of the needle, you try to create a little minor injury, what happens if that area is reinjured or reinfected for any reason just in the course of life? What happens when the cells die? Is there any toxic effects that could happen from that?

Then I guess the third question is it also gets to mechanism. It's kind of interesting that you're treating a problem of aging with autologous fibroblasts that themselves are aged and promote and working on endogenous collagen which also is aged.

So is there an age cut-off where you wouldn't do this because the collagen itself and the cells themselves will not give you this response, and have the data ever been stratified like that and would you recommend an age cut-off?

Also, with regard to tumor genesis, would you recommend that a patient who already has this history of basal cell carcinoma or something like that not put their cells back into that area in response to an injured area?

DR. NOVAK: With regards to the tumor genicity issue, I think at this juncture we have excluded basal cell carcinoma, for example. We think that's a prudent approach. It's not that we're concerned about again the skin necessarily behind the ear transferring any sort of a tumor-genic cell or being selected for in culture. That's not our issue. Again, it's just primarily an issue of good practice since basal cell carcinoma has a fair frequency and, in general, why have that risk if you already have a history of basal cell carcinoma?

With regards to aged cell, the aged cells

concept -- and when we recommend a cut-off for the treatment or the use of this particular product. Again, in our studies we had subjects into their late 70s and 80s. You can see from the stratification, which will be discussed later, I believe, by our colleagues at the FDA, the data; again, we also presented it. We don't have large numbers of individuals who are older, but when we've looked at a couple of parameters. I'm just going to culture those cells, we don't necessarily see any differences. So from a production point of view, we don't know that age is going to be an issue for production and that's one key factor for this therapy. Even if you wanted to treat this group, can you make the product, and the answer is yes.

With regards to effectiveness, does it scientifically or biologically make sense with aged cells to grow those out and give those back to people. And, again, an aged skin environment, we believe that's the case and we haven't put any upper limit restrictions on the product to date. However, as we collect more information, certainly we'd be looking

carefully to see what correlates there might be.

Again, as far as biology, we could have discussions around resetting the clock. Is that done when you take a fibroblast from in situ from a biopsy into culture? Again, those discussions are more theoretical and we don't have any evidence for that one way or the other.

And last, no, we don't believe -- upon injection, we don't believe the cells die. In fact, it's likely that the viability does decrease for some percentage of the population of cells injected. That seems quite likely. And it may be the result of some of our adverse events at the local reaction. But we also believe a percentage of those cells stay viable.

Migration is a relative term. We think they stay local in the area of injection, as evidenced by our clinical data, also as evidenced by preclinical data in the literature. And I'll stop there, if I've answered all of those.

DR. GERSON: Ms. Rue.

MS. RUE: I really do have one question. You said that there was a proximate 90-day between harvest

and reinjection.

Is there any process in place for rescreening or health update? I don't see that that was mentioned as it's related to possible adverse effects or just anything about the client.

DR. NOVAK: Yes. Thank you. Actually, it's 90 days from the time of biopsy to an injection back to the patient. So the culture time is approximately, again, on the average of 50 days.

Was there additional screening? Of course, when a patient comes back in in a clinical trial, they were evaluated by their physicians for any emergence of new adverse events, which would include, for example, presentation of basal cell carcinoma or any other, again, overt change in health status. No other screening was done, other than, again, what would be routine and expected for the clinical evaluation prior to that injection.

DR. GERSON: We will need to take a break at this point. The FDA presentation will be made right thereafter. I'd like to make sure that we're at the podium at 11.

Thank you.

(Whereupon, a recess is taken.)

DR. GERSON: The FDA will present their response and perspective of the product review, beginning with Dr. Thomas.

Thank you.

DR. THOMAS: Thank you, and good morning. My name's Terrig Thomas, and I'll be leading off the presentations, providing the FDA perspective on Azfibrocel-T for the treatment of moderate to severe nasolabial fold wrinkles.

The name Azfibrocel-T is the official United States adopted name that was assigned to the product a couple weeks ago, but during some of our presentations, you'll see it still referred to by its old name Isolagen Therapy or IT. A trade name has not yet been approved for the product.

The following FDA presentations are designed to provide the committee with our perspective on the data submitted to the BLA and hopefully facilitate discussion of the questions we have asked.

I'm Chair of the BLA Committee and I will be

presenting for the product manufacturer. This will be followed by two clinical presentations. Dr. Lim will present for clinical efficacy and then Dr. Zhu for clinical safety. Finally, Dr. Lee will present her presentation for the statistics.

Before I begin, I want to acknowledge other members of the BLA Review Team and to emphasize that this has been a multidisciplinary effort.

So as we've heard, Azfibrocel-T is an autologous cell product, composed primarily of a suspension of viable cultured cell fibroblasts expounded from a patient's skin biopsy. During my presentation, I will provide a little bit more information to you about the manufacturing. I know there were some questions earlier. So within the scope of the ability to talk about things in this kind of environment, I will provide as much information as I can.

I will first talk about the source material used in the manufacture. I'll give you a review of the manufacturing process and then go through some of the cellular characteristics and final product testing that

are relevant to the safety of the product, and finally comment on the potency assay.

So the source material, as we heard, is a post-auricular biopsy. The biopsies are performed in the physician's office where three 3 millimeter punch biopsies are taken and placed in sterile medium before being shipped overnight to the manufacturing facility at 2 to 8 degrees Celsius.

So this slide shows an overview of the manufacturing process and I shall go through it slowly, step by step. And once the cells arrive at the manufacturing facility and are checked for any signs of any gross contamination, cells are isolated from the biopsies and placed into a tissue culture vessel.

The cells are then expanded through two to three passages until sufficient cells are obtained for each of the three sets of injections required for treatment. During this time, the cells are routinely monitored for morphology and I will come back to that point a little bit later.

So once sufficient cells have been obtained, they are harvested, washed, resuspended in

cryopreservation medium, and then frozen down until all testing has been completed. The tests conducted on the cells are shown here and I will go through those again individually a little bit later.

Once all the testing has been completed, the cells are cleared for release to the clinical site. However, due to the nature of the cells being a living cell population, they're not sent to the clinical site until the day before they are needed. So once the testing is completed, the physician is noted and a patient appointment is made. And then, when required, the cells are thawed, washed, and formulated in an acitonic medium called Dulbecco's Modified Eagle's Medium to a final formulation of one to two times 10 to the 7th cells per ml.

So by now, any process-related impurities, such as serum or cryopreservative, will have been removed from the cells or reduced to residual levels.

A final set of tests is then performed on the final product before shipment, including sterility and potency, and then the cells are shipped to the clinical site overnight at 2 to 8 degrees Celsius. So the whole

process from the collection of the biopsy to the shipment to the physician for the first treatment is approximately 90 days or three months.

One point I wanted to make here is that during the clinical trials, the control groups received injections of the DMEM alone without cells. So this cannot be considered as a true placebo. That's why we call it a vehicle control.

So the next few slides, I'm just going to briefly describe some of the morphology and cellular characteristics of the cells I studied from the biopsies that are relevant to the safety of the product.

Fibroblasts proliferate more rapidly in vitro than other dermal cell types, such as keratinocytes, melanocytes, adipocytes, et cetera, and represent, as we have heard, greater than or equal to 98 percent of the cells in the final product. Keratinocytes comprise up to 2 percent of the product.

As I mentioned earlier, cell growth and morphology are monitored throughout the cell expansion phase to distinguish abnormal fibroblasts from

transformed fibroblasts and other cell types, and any cultures exhibiting abnormal growth or morphological characteristics are discarded. It should be pointed out that during the pivotal trials, there were no reported occurrences of abnormal morphology during the manufacture of Azfibrocel-T.

This slide shows some of the tests that are performed on the cells to assure their sterility, their viability, and their consistency prior to shipment to the clinical site. Sterility is measured by an absence of micro-organisms and microplasma and endotoxin levels below an established acceptance limit. As we've heard, there's a proprietary identity test performed on the cells to ensure that they are greater than 98 percent fibroblasts.

The potency assay is a combination of cell count, cell viability, and the collagen content or collagen production. I'm just going to mention a bit more about the collagen production in the next slide.

So the mechanism action of Azfibrocel-T has not been defined; however, the rationale for collagen production as part of the potency assay is based on the

premise that collagen is a primary component of the tissue and a major acellular matrix protein synthesized by fibroblasts, and that fibroblast survival and collagen biosynthesis are proposed to be important factors for Azfibrocel-T improvement to the nasolabial fold wrinkles.

So in summary, whereas there are no specific questions on the manufacture of the product being proposed to the committee, there may be elements of the manufacturing process that are relevant to the clinical discussion of safety and efficacy questions.

Thank you very much.

The next speaker will be Dr. Lim.

DR. LIM: Good morning. I'm Agnes Lim. Dr. Zhu and I will present the clinical reviews for this BLA.

I will begin my presentation with an overview of the two pivotal studies, Studies IT-R-005 and 006. They were identical protocols conducted under a special protocol assessment agreement with the FDA. Study results will then be presented. I will present the efficacy results. The safety results will be presented

by Dr. Zhu.

The proposed indication is treatment of moderate to severe nasolabial fold wrinkles in adults. The study title is shown here. They were multicenter, double-blind, one-to-one randomized, and vehicle control.

IT administrations were given at three treatment visits, each visit five weeks apart. The control, called a placebo in the studies, was the vehicle medium only without the fibroblasts. Control was injected exactly the same way and in the same volume as IT.

The pictures provided by the sponsor depict the treatment injection procedure. After a treatment area was identified, a 29-gauge needle was injected into the papillary dermis, parallel to the skin surface. When done correctly, the shadow of the needle should be visible under the skin, as depicted in the middle picture.

On withdrawing the needle, boluses of IT at the pre-specified dose were injected. Blanching of the injected area, as shown in the last picture, indicate

that IT was correctly injected.

This and the next slide show the two wrinkle assessment scales that were used in the studies for the evaluation of the primary efficacy. Both were live assessments.

The first scale, the subject wrinkle assessment, is shown here. It is a 5 point scale graded by the subject in response to the question, how do you feel about the wrinkles in the lower part of your face today. To be eligible for the study, the subject must be dissatisfied, which is a minus 1 the scale, or very dissatisfied, corresponding to a minus 2.

The second scale was the Evaluator Wrinkle Severity Assessment. It is a 6 point scale that was used with a photo guide shown on the right, and it was based on the Lemperle Facial Wrinkle Severity Scale. To be eligible for the study, both sides must be graded three or worse at screening and baseline. Recall that the scale was administered by masked evaluators in a live assessment of the subject.

This is an outline of the key eligibility

criteria. Subjects must be 18 or older, have met both the subject and evaluator wrinkle severity gradings, and have a suitable site behind the ear for biopsy.

Exclusions include a total treatment area that exceeded 20 centimeters in length, along with a number of pre-specified skin conditions and previous facial cosmetic procedures or dermal products used. Subjects with present or past history of basal cell carcinoma were excluded. The treatment schema will be shown in the next slide.

After entrance criteria were met, skin biopsies were performed at the baseline visit. Once a biopsy was determined to be acceptable, the site was notified and the subject randomized.

For a given subject in the study, the injector and the evaluator were different investigators. The primary efficacy evaluation took place at six months following the last injections using pre-specified co-primary endpoints. Safety was assessed at each study visit and a final safety assessment was conducted by telephone at 12 months following the last injection.

The two co-primary endpoints for efficacy are

shown here. For the Evaluator Wrinkle Severity Assessment, wrinkles must be Grade 3 or worse at baseline. Success at six months must show a two point or better improvement on both sides. For the Subject Wrinkle Assessment, the grading must be either a minus 1, dissatisfied, or a minus 2, very dissatisfied, at baseline, and success at six months was also defined as a two point or better improvement.

This and the next slide show the secondary endpoints. The primary analysis of all secondary endpoints were analyzed for the ITT population in the same manner as the co-primary endpoints. Here, as secondary endpoints, the Evaluator Wrinkle Severity Assessment and the subject wrinkle assessments were evaluated at visit three, four, and five intermediate visits.

The second set of secondary endpoints was the evaluator improvement assessment and the subject improvement assessment. In these assessments, photographs taken at visits three, four, five, and six were compared to the photos taken at baseline. The assessments were performed at visit six and no photos

were reviewed prior to visit six. The evaluator rated the wrinkles changes on both sides while the subject rated wrinkles changes in the lower part of their face. Both evaluator and subject use a similar 5 point scale shown here and success was defined as a one point or better improvement.

All of the secondary endpoints achieved nominally significant statistical significance. Dr. Lee will further discuss this in her presentation.

This slide outlines the statistical plan. The population for the primary efficacy analysis was the ITT population, which included all subjects randomized. The modified intent to treat, the MITT population, were subjects who received at least one treatment. The MITT was used for the safety analysis.

The third population, the efficacy evaluable, were patients who met entrance criteria, received all three treatments and had no major protocol violations. The studies were powered at 80 percent at a 0.5 significant level. Sample size was based on assumptions of a response rate of at least 40 percent for IT and a response rate of less than 20 percent for

the vehicle control.

The missing data were imputed as treatment failures for both IT and control. The primary analysis plan and sensitivity analysis and analysis of the secondary endpoints will be discussed in the statistical presentation.

I will now present the study results for Study 005 and 006.

The enrollment for the two studies is shown on this slide. In Study 005, a total of 203 subjects were randomized in a one-to-one ratio. In Study 006, a total of 218 subjects were randomized. Each study took approximately two years to complete at a total of 13 sites in the U.S. for the two studies together.

The detailed demographics for the ITT population, age, gender, race, and ethnicity for each study, are shown here. This table shows a number of differences among the demographic categories. I will highlight the key differences in the next slide.

First, the demographics between the two studies were similar. The median age was 56. Ages ranged from 23 to 81. However, only 6 percent were age

40 and below and 17 percent were age 65 and older. Ninety percent of the study subjects were female. The demographic for race were 92 percent white, 1 percent African American, and 1 percent Asian. The demographic for ethnicity was 10 percent Hispanic/Latino.

The disposition of subjects for each study is shown on this slide. In both studies, more subjects terminated the study early in the treatment group than the control group; specifically, 18 percent in the two studies for the IT group versus 12 percent in the control group.

Looking at the reasons for early termination, the two main reasons were subject withdrawal and sponsor request. When early termination was by the sponsor’s request, the main reason was due to IT manufacturing failure. Details of manufacturing failure will be shown in the next slide.

The total IT manufacturing failure rate for the two studies was 11 percent. There were two types of IT manufacturing failures: where no products were produced or insufficient products. The total rate for not producing any IT product in the two studies was

about 6 percent, the total rate for producing insufficient IT product in the two studies was about 5 percent. An IT control subject pairing procedure in an attempt to maintain randomization and study blind for manufacturing failure was initially used but was later modified, which accounted for the imbalance in the manufacturing rate for IT versus control, as you can see on the screen.

Success rate for the co-primary endpoints for Study 005 and 006 are shown on this slide. In the Evaluator Wrinkle Severity Assessment, 33 out of a 100 subjects in the IT group responded versus seven out of 103 in the control group in Study 005. In Study 006, 21 out of 110 subjects in the IT group responded versus 8 out of 108 in the control.

For the second co-primary endpoint, the Subject Wrinkle Assessment, 57 out of 100 subjects in the IT group versus 31 out of 103 in control in Study 005 responded. For Study 006, 50 out of 110 IT subjects responded versus 19 out of 108 in the control group.

The magnitude of effectiveness between the two

studies, this will be further discussed in the statistical presentation.

In summary, the efficacy conclusion for the pivotal studies are both co-primary endpoints at six months were met in each of the pivotal studies. Results of the secondary endpoints were supportive with the caveat previously mentioned about the nominal statistical significance with these endpoints.

The efficacy of IT beyond six months has not been demonstrated and, finally, no studies have been conducted for repeating treatment cycles of IT.

Dr. Zhu will now present the safety results.

DR. ZHU: Good morning. I'm Yao-Yao Zhu, clinical reviewer. I'm going to present the safety results.

Here's the overview of my presentation. First, I will present safety data from the two pivotal trials, 005 and 006, followed by the analysis from the seven clinical trials. This also includes 005 and 006. Data from the seven trials will be called integrated safety data.

This table summarizes the information of the

safety population, which is defined as all subjects who received at least one injection of either active component or vehicle control.

508 subjects in the treatment arm in the integrated safety population also include 41 subjects who cross over from control arm to the treatment arm in early studies. And later on, I will briefly discuss the safety data from the commercial experience.

The study timeline for the safety monitoring is emphasized here in this slide for 005 and 006. Safety assessment was done at each visit where patient self-reporting of adverse events as well as physician observation and follow-up took place. However, no formal mechanisms in the forms of patient diary or patient questionnaire regarding reporting adverse events were described in the study protocol.

During visit one, two, three, the subject received treatment injection as well as safety monitoring. After the treatment was completed, there were three additional visits for efficacy assessment as well as safety monitoring and they’re two months apart.

The final safety follow-up was conducted by a

telephone call at 12 months following the last treatment injection.

I should emphasize here that the safety observation intervals were five weeks apart during the treatment visits where the majority of adverse events related to the treatment injection occurred during this period, as we recall from previous presentation. Therefore, the spacing of the safety observation intervals may influence the frequency of the reporting of adverse events.

The length from visit one to visit six was a total of 34 weeks that was called acute study. The 12 months telephone call was called a long-term study.

The next three slides will summarize the safety data from Pivotal Trial 005 and 006. The treatment emergent adverse events were categorized as either all adverse events or injection site events. I'll focus on injection site events.

Please note that the subjects in the control group receive a vehicle injection and similar adverse events occurred in both the active group and the control group. Therefore, the control was not a true

placebo. This is true for all the trials here.

Overall, about 60 percent of subjects reported adverse events in all organ system classes in both groups. Now I will focus on an injection site condition that were mainly considered to be related to treatment injection.

Now, about 30 percent of subjects in both groups reported injection site reactions. Among those reactions, erythema and swelling were the majority of the events. That was at higher frequency in the active arm. However, for injection site bruising, there was a reversal effect where the control arm had a higher rate, as we noticed before.

This table demonstrates adverse events in Study 006 in a similar manner. Similar proportions of subjects reported total adverse events as well as local events as compared to 005. As I highlighted here, in addition to high incidence of erythema, injection site hemorrhage occurred in 10 to 15 percent subjects, but all bleeding events resolved within the same day of the injection. The data is not showing here.

There was also a reversal trend with the

injection site hemorrhage as well as bruising, where the control group had a higher rate, as I highlight here.

Now, this is not an easy table and I will go column by column, each item briefly. This table shows all the adverse events, injection site events, and the non-injection site events that occurred in less than one percent safety population in 005 and 006. These were considered related treatment injection by the investigators.

There was a total of nine cases in 005 and three subjects or five events in the 006. Why five events? Because in the case of eyelid edema, this is the third row from the bottom, there was three similar events of each of the three injections, and the edema occurred. And two events resolved within a week and one was ongoing by the end of the trial, as I highlight here. I'm going to talk about it later.

The other types of adverse events, including basal cell cancer, which I'm going to discuss in the next slide in detail, and the flare of a herpes simplex in lips, and the probable facial allergic kind of

reactions, such as eyelid swelling, change of sensations on the injection site, and then post-procedural discomforts, such as headache, as listed, are the preferred terms.

I show here some events lasted for weeks and some even for months. And one was ongoing by the end of the trial, and that I mentioned earlier. And then they were mild and moderate in severity and four events needed some medical and surgical treatment.

This slide shows the case of basal cell cancer in a 76-year-old white female subject. This subject had no previous history of skin cancer, but at her baseline visit, sun damage in the skin was documented. She received three Isolagen treatments in Study 005.

At seven months, after her first treatment, a nodule the size of 0.4 by 0.4 centimeters was found in her right upper lip area near the injection site. The biopsy confirmed that it was a basal cell cancer. It was excised by Moh procedure and no recurrence in the follow-up visit one and a half years later after the surgery. The investigator considered this event possibly related to the treatment injection.

Other documented adverse events for this subject were trends in local erythema and swelling right after the injection lasting for three days. A solar keratosis lesion on the bridge of her nose was diagnosed and treated with liquid nitrogen at the same time with a diagnosis of basal cell cancer.

There's one case of basal cell cancer on the shoulder I'm not going to discuss here.

Now I will present integrated safety data, and, remember that's the combination of seven trials, including 005 and 006. And also I'm going to go briefly column by column.

So this table summarized the main features of the study design of seven clinical trials and listed here in chronological order. This included three Phase II trials and four Phase III trials, the two pairs, as we mentioned before, 003-B, A, and then 5 and 6. Those four pairs actually comprise 70 percent of all safety populations.

All of the studies were randomized, double-blind, vehicle control, except for Study 007, which was an open label trial. Now Study 001 was designed for

testing three labels, dose labels, for determining the appropriate dosing for the later trial. The rest of the six trials used a similar dose at 10 to 20 per cc, per ml.

The safety observation period, the third column, includes an acute study phase, varying from four months to six months, and a long-term follow-up period. The total length was about a year, more or less a year, in all trials.

The integrated safety population, including 467 subjects in the active group and 354 in the control group, a total of 821 subjects. And these are not including the 41 subjects crossed over in early trials.

The treatment intervals, that means between the two treatment injections, increased, varied from the trials, and the increase between one to two weeks in early trials to four to six weeks in the later trials, mainly the 005 and 006, as we presented before and for the purpose of decreasing adverse events and increasing the fibroblast growth in the injection site.

However, as I mentioned before in the previous slide for the period of the trial, the spacing of the

safety observation may affect the accuracy of the safety data collection without the formal mechanism for safety data collections, such as patient diary, questionnaire, and maybe there's a dilution effect.

The amount of treatment areas were also decreased, vary from trial to trial in the early trials, up to 14 areas, talking about a symmetrical area, in early trials, to only two areas in the pivotal trials. Overall, these trials varied somewhat in size and location of the injection site as well as the treatment intervals and the safety observation intervals.

This table summarizes the injection site reaction in more than 1 percent integrated safety population, the seven trials. The frequencies of all the injection site adverse events from the seven trials were tabulated for both treatment arms. Overall, 67, two-thirds, of the Isolagen or active subjects reported injection site adverse events, while 40 percent in the control group.

I will discuss this finding in the next slide with comparison to the two pivotal trials, 005 and 006.

As for the types of adverse events, the majority of local adverse events were injection site erythema, bruising, swelling, and pain, as listed here and highlighted here. Erythema and swelling occurred more frequently in active subjects than control subjects.

Regarding the injection site nodules, there were no details for their definition and the histology. They were all graded as mild in severity and resolved within two weeks without medical intervention. Four nodules were reported in 005 and 6. The rest of the other 19 cases of nodules were documented in the other trials.

Now, this is a comparison I mentioned before. This table demonstrates the frequencies of injection site adverse events in the two pivotal trials as well as integrated safety data, the summation of seven trials.

In comparison, subjects in Study 5 and 6 reported a lower incidence of injection site reactions, about 30 percent, actually pretty balanced between control and active patients, versus about 60, up to 67

percent in the integrated safety population.

The underlying reasons for decreased frequency of adverse events in 005 and 006 may be due to one or combination of the following factors. For example, increasing treatment intervals, enhanced physician training for injection techniques, and a decreased exposed area, injection areas, as suggested by the applicant.

As I mentioned previously, the increasing spacing of clinical observation intervals in the pivotal trials may play a role in decreasing reporting detection of adverse events.

This is a list of adverse events that occurred in less than 1 percent of safety population in either the injection site or non-injection site, and these were considered related to treatment injection by the investigators.

The examples here, I clustered some of them, of the adverse events are probable facial allergic reactions, such as rash, eyelid and facial edema, and a flare of herpes in the lips, and a change in the skin sensation, either hypersensitivity or numbness, and the

post-procedural discomforts, such as dizziness, headache. And these events occurred more frequently in the Isolagen group.

The severity of the local adverse events were graded according to common term logic criteria for adverse events published by National Cancer Institute, National Institute of Health.

This table shows that 82 percent of local reactions in the active group was mild in severity. However, there were six cases of severe local reactions as listed here, five in the Isolagen group and one in the control. All resolved within 10 days -- and no one withdrew from the study due to the severe adverse events. I should mention here that there were no serious case reports related in the treatment injection.

Now regarding ischemia, there’s one case here, a severe case, and there’s a total of three cases of skin ischemia reported in the early study, 002 and 003-B. The other two cases were graded as mild, and this is as severe, and these were described by the investigator as interruption of local blood supply and

a dusky in appearance. The three events resolved within two days and one of the events, the case listed here, required aspirin and oxygen in the office.

Now duration. This table shows the duration of local adverse events in an integrated safety population. The first column categorizes the duration at different intervals of days and the second and third columns display the numbers and the percentage of adverse events within each time intervals of the injection in active and the control arms.

Please note the numbers here are the events, not subjects.

Within seven days of the injection, about 85 percent adverse events resolved in active group, about 90 percent in the control group. By day 30, there was about 5 percent events remaining in the active group and 2 percent in the control group. By the end of the study, that is about 12 months later, there were five events ongoing, all in the active group.

I'm going to describe those ongoing cases in the next slide.

This table -- again this busy table, I'm going

to go column by column, each item briefly -- demonstrates the five ongoing cases. There was almost one case in each trial, except Study 003-B and 007. Three adverse events occurred at injection site with persistent swelling and numbness, and two events occurred at different sites, other than injection, and one, for example, eyelid and hair, alopecia case. The injections, as we see, because it involved different trials, were at different area of the face.

Now two events occurred on the same day of the treatment and all the events were graded as mild in severity. Three events did not require an intervention but two events needed some medical treatment.

Now I'm going to present the demographic distribution in the integrated safety population.

Similarly to the Study 005 and 006, there were three groups that were underrepresented in the integrated safety population. They are groups of geriatric, subjects more than 65 years old, male, and non-white. Each of the subgroups was comprised of 90 percent of total population. Therefore, the sample sizes in the subgroups were small and limited to draw

safety conclusions. Each group had similar types of adverse events as in integrated safety population. No special types of adverse events reported, such as keloid formation, in this limited population.

I'm going to briefly mention the commercial experience. As we mentioned, the product was exposed to the subjects in the United Kingdom and Australia. Only the United Kingdom and United States have safety data, so that's what I'm presenting here.

This slide summarizes safety information from commercial experience and please note the applicant initiated IND for the product in 1999. During this commercial period, several thousand subjects were exposed to the product in the United States and United Kingdom. However, safety monitoring, recording and reporting were very limited. The collection of adverse events were based on some retrospective chart review in the United States and limited registry in the United Kingdom after 2004.

Similar local adverse events were described for those subjects as listed here, and there was three cases of serious adverse events reporting, including

two cases of systemic allergic reaction, edema, and also the anaphylaxis, and a case of lump on the eyelid requiring surgical removal. The history of that shows a fibrous overgrowth.

In summary, for the integrated safety population, adverse events in more than 1 percent safety population are mostly local injection site reactions. I've listed here and discussed in detail in early slides.

Adverse reactions in less than 1 percent -- that's including injection and non-injection, local injection site -- probable facial allergic reactions, flare of a herpes simplex in the lips, change of skin sensations and post-procedural discomfort.

Most adverse events are mild and moderate in severity. Most adverse events resolve within two weeks, but 5 percent events lasting beyond 30 days, and there were five unresolved cases. One case of basal cell cancer near injection site was diagnosed. Two cases of systemic allergic reaction were reported in United Kingdom in a commercial experience. Sample

sizes are small in all subgroups and the safety observation period was between 12 to 15 months.

This is the end of my talk. Now, Dr. Shiowjen Lee will present the statistical analysis of the pivotal trial.

DR. LEE: Thank you.

Good morning. In this presentation, I will cover efficacy review in the two pivotal trials from statistical perspective, and for safety results of the study, Dr. Zhu has presented.

The outline of my presentation is the following. First, I will present the overall efficacy findings of IT compared to vehicle in the co-primary efficacy endpoints. I will mention briefly about the efficacy in secondary endpoints, followed by some issues identified in the findings, including different success rates in the co-primary Evaluator Wrinkle Severity Assessment endpoint and study size and efficacy in some subgroups, and finally a summary of the presentation.

To remind you that for efficacy assessment in the two pivotal trials, the co-primary efficacy

endpoints are percentage of patients who had at least a two point improvement from baseline to six months in the Evaluator Wrinkle Severity Assessment and in Subject Wrinkle Assessment. Each study is declared as a success if IT is shown to be superior to vehicle with respect to each co-primary efficacy endpoint. Results of the co-primary efficacy endpoints are presented in the next slide.

Results shown are based on the intent to treat analysis with missing data imputed as failures in both treatment groups applied with Cochran-Mantel-Haenszel test to stratify by site. This was the pre-specified primary analysis for the two pivotal trials.

As you can see from the table, IT is statistically superior to vehicle with respect to each co-primary efficacy endpoint for each study. And I would like to point out here the Study 005, the success rate in Evaluator Wrinkle Severity Assessment for Study 005 and Study 006 is all below 40 percent, and the vehicle group had about 7 percent success rate in Evaluator Wrinkle Severity Assessment. And on the other hand, for the success rate in Subject Wrinkle

Assessment, both studies show about 40 percent success rates, while the Study 5 has 30 percent success rate in vehicle group and 18 percent for Study 6.

To summarize the overall efficacy here, the observed treatment effect in success rate of Subject Wrinkle Assessment endpoint is 27 percent for both trials. On the other hand, the observed treatment effect in success rate of evaluator assessment endpoint is 26 percent for Study 5 and 12 percent for Study 6. There's a difference in treatment effect in success rate of Evaluator Wrinkle Severity Assessment endpoint between the two trials.

Additionally, I would like to point out here is, as mentioned previously by Dr. Lim, the trials were originally designed to detect a minimum of 20 percent treatment effect, assuming vehicle had less than 20 percent and IT had at least 40 percent success rate.

Although the observed treatment effect appeared to meet what was the design in three out of four percentage numbers, the success rates in the individual co-primary efficacy endpoints actually were not anticipated at design stage. For example, the

success rate in Evaluator Wrinkle Severity Assessment endpoint were all below 40 percent for both trials, as shown in a previous slide.

The overall efficacy results of the co-primary efficacy endpoint generally is robust because of the following. Conclusion based on the modified intent to treat and efficacy evaluable analysis are in agreement. Conclusion based on different statistical method for analysis are in agreement. For example, the repeated measure and analysis takes into account data over visit and time to event analysis from a different angle looking at the data. Here, the event means at least a two point improvement sustained for six months. All analysis showed the superiority of IT to vehicle.

Thirdly, different ways of handling missing data in ITT analysis generally result in the same conclusion, but because the missing data are already arranged from 9 percent to 20 percent among the treatment groups, results are not statistically significant for the worst case scenario -- the worst case impute a missing in the vehicle as successes and the missing data in the IT group as failures. However,

IT is numerically better than vehicle in this narrow scenario.

Efficacy of the secondary endpoint will be presented in the following three slides as detailed results are included in the AC briefing document. I will go over them very briefly.

In addition to the co-primary efficacy endpoint, several secondary endpoints were pre-specified in the protocol to evaluate the IT efficacy, including the following: success in Subject Wrinkle Assessment at the intermediate visit, namely visits three, four, and five; success in Evaluator Wrinkle Severity Assessment at visit three, four, and five; at least a one point better in subject improvement assessment at month six based on photos; at least a one point better in evaluator improvement assessment at month six based on photos.

To remind you, the scales of subject improvement assessment and evaluator improvement assessment are different from those of the co-primary efficacy endpoints, and photos were used for these evaluations as presented previously by Dr. Lim.

Upon meeting the objectives of the co-primary efficacy endpoint, for possible label inclusion and to preserve the overall false positive rate for testing secondary endpoint, the statistical analysis plan tested the following secondary endpoints in hierarchical order. They are listed on these slides.

As you can see, they are slightly different from those in the previous slide.

The last two, time to sustained success, were included in the stat analysis plan for label inclusion while the Subject Wrinkle Assessment and the Evaluator Wrinkle Severity Assessment at intermediate visits were not included in the statistical analysis plan for labeling plan.

For testing in hierarchical order, endpoints listed on this slide would be tested sequentially in order till the end or when IT is not statistically superior to vehicle at certain point. The procedure would then stop and no further testing.

This slide gives you the summary of the secondary endpoint. IT is statistically superior to vehicle at month six in subject improvement assessment

and evaluator improvement assessment, both based on photos. Time to sustained success and Subject Wrinkle Assessment and Evaluator Wrinkle Severity Assessment analysis support the outcomes of the co-primary endpoints.

Subject Wrinkle Assessment and Evaluator Wrinkle Severity Assessment at intermediate visit, visit three, four, and five, were not included in statistical analysis plan for label inclusion.

Now, I will be switching gears back to the co-primary efficacy endpoints. Although results of the co-primary efficacy endpoints showed the superiority of IT to vehicle, there are some issues identified. They are presented in the remaining slides of the presentations.

In Study 6, success rate in Evaluator Wrinkle Severity Assessment endpoint are smaller for IT group at three sites as shown on this slide as compared to other sites. These three sites accounted for about 55 percent of study population. Because of this issue, the overall success rate in Evaluator Wrinkle Severity Assessment endpoint for Study 6 is considerably lower

than that for Study 5.

Secondly, co-primary efficacy findings in subgroups, in particular the non-white, the male, and the elder populations, the non-white and male population are underrepresented in the two pivotal trials, while numerical reverse efficacy trends were observed in elder population.

It should be pointed out that, as presented previously by Dr. Zhu, there are limited safety information in these subgroups, as well. First, we'll talk about the issue of low success rate in Evaluator Wrinkle Severity Assessment endpoint at three sites in Study 6.

This table summarized the success rate of Evaluator Wrinkle Severity Assessment endpoint by study site for the two trials. As you can see, this is the Study 6, and the yellow highlighted spot would be those success rates in Evaluator Wrinkle Severity Assessment for the IT treatment.

These three sites, the success rate is lower as compared to the remaining sites, on average about 7 percent compared to 35 percent for the remaining sites.

In fact, if you take a look at the vehicle group for these three sites, apparently they seem to be also relatively lower compared to others.

So because of this issue, the overall success rate in the Evaluator Wrinkle Severity Assessment endpoint for IT group is 19 percent for Study 6 as compared to 33 percent for Study 5. Given that, the overall success rate of vehicle is 7 percent in both trials.

We have examined the patient characteristics across sites. Factors of age, baseline wrinkle severity, missing data array and injection volume cannot explain the low success rate in evaluator assessment endpoint at these three sites. Therefore, the investigator evaluation may be a potential factor.

In order to examine the impact of these three sites to the results of the study, here is the table presenting the outcomes of the co-primary efficacy endpoint for the three sites as compared to the remaining sites.

The treatment effect in the Evaluator Wrinkle Severity Assessment at the three sites is about four

percent as compared to 23 percent for the remaining sites. On the other hand, the treatment effect for the Subject Wrinkle Assessment for the three sites is about 33 percent as compared to 21 percent for the remaining sites.

Sensitivity analyses are performed. Results show that IT is statistically superior to vehicle in success rate of subject assessment endpoint for the three sites as well as the remaining sites for the success rate in Evaluator Wrinkle Severity Assessment endpoint. IT is superior to vehicle for the remaining sites but not for the three sites alone.

The next three slides will summarize the subgroup efficacy results. It should be noted that subgroup results are intended to observe trends. The studies were not designed for inferentially statistical comparisons between treatment arms within subgroups.

Efficacy subgroup results were females and white subjects, which is similar to the ITT analysis because the study population was predominated by female and by white subjects.

Consistent efficacy trend of IT and

numerically better than vehicle generally is observed for the subgroups of male, baseline wrinkle length, baseline Evaluator Wrinkle Severity Assessment endpoints, and a baseline Subject Wrinkle Assessment. However, evidence of IT efficacy is limited for male, which accounted for 9.7 percent of study population, and the non-white is about 8 percent study population as they are underrepresented.

This slide presents the subgroup efficacy results by age for Study 5. Five age groups are considered in this slide. The values in the parentheses in the last two columns are the success rates for the co-primary efficacy endpoints within subgroups.

It can be observed that efficacy trends favor IT treatment for all age groups, except the age group of 65 years and older, in Evaluator Wrinkle Severity Assessment endpoint, a numerically reverse efficacy trend with success count difference of one.

Similarly, this slide showed the subgroup results by age for Study 6. Efficacy trend favors IT treatment for all age groups, except the age group of

65 years and older, for the Subject Wrinkle Assessment endpoint, which is different from the previous slide in Study 5. Study 5 has the issue about the Evaluator Wrinkle Severity Assessment. But again, here, numerical reverse efficacy trend with success count difference of one. Elder subjects accounted for 17 percent of study population in the two trials.

Summary of the staff presentation. IT is statistically superior to vehicle regarding the treatment success in Evaluator Wrinkle Severity Assessment and Subject Wrinkle Assessment for each study.

Results of the secondary endpoints support the outcomes of co-primary endpoints. Evidence of IT efficacy for male and non-white subjects is limited because of underrepresented subgroups, observed numerically reverse efficacy trend in different endpoints for the two trials in elders, such as aged 65 and older. Efficacy of IT beyond six months has not been established.

Thank you.

DR. GERSON: Thank you very much. I would

like to thank the FDA review group for its excellent presentation and for the questions that it's raised for us to further consider.

If I could take the chair's prerogative, it is now a little after five past 12. To help us navigate through the next hour, I would like to ask now whether there are members of the audience who would like to make a presentation during the open public hearing opportunity and, if so, to at least raise their hands now so that I can gauge how we might spend the next hour.

Seeing none, I will allow us to then spend this next hour to review the two presentations that we've had, focusing first on questions that were raised by the FDA presentation.

Go ahead, Dr. Burke.

DR. BURKE: I have two questions. One is that it seems that the adverse effects were primarily within the first week. I mean many of them resolved within three to seven days. And the presenter also showed that there seemed to be fewer adverse effects when there were larger intervals between the treatments, and

I just want to suggest that, first of all, it might have been wise, having seen that kind of effect, that each patient should have been evaluated within a week of the treatment always, and perhaps if there's a longer interval between treatments, the patient really didn't remember the transient adverse effect. But it's good news that the effects were transient.

The other thing is that the two of the three severe reactions, the anaphylaxis and the angio-edema, was there any attempt to see if those patients were allergic to penicillin, because if those two reactions were in the U.K. where there was possibly penicillin in the media, that's obviously extremely significant.

DR. WITTEN: I think we'll refer that question to the sponsor.

DR. GERSON: Could the sponsor respond?

DR. SMITH: About the two cases of anaphylaxis or systemic hypersensitivity in the U.K., one of those cases was ruled by the treating physician to be either due to lidocaine or latex and not be due to the Azfibrocel-T product. The other was felt to potentially be due to that product. But I don't know.

There was no further follow-up on whether that patient was penicillin allergic or not.

DR. BURKE: And could I just ask one little follow-up? I know that there are many steps between the fibroblast proliferation, which presumably has some growth factors and other things in the media, including serum, and the question is what was the placebo, and could any of those growth factors or serum have been in the final product?

Did the placebo possibly have those materials? That's question one. Because that might have accounted for some of the efficacy of the placebo. But also, it might have caused the severe reactions.

DR. MASLOWSKI: Just to reintroduce myself, I'm John Maslowski. I'm the vice president of Operations at Fibrocell Science, so I'm employed directly by the company.

The first question, the vehicle was actually the carrier media with no added protein or anything. It's simply just a media-based carrier with the cells directly in it. So there are no additional growth factors or protein. We used no protein from the

cryopreservative on, so there's nothing -- it's not formulated with any sort of sera or any other growth factor prior to injection.

DR. GERSON: Dr. King.

DR. MASLOWSKI: That's also the same, by the way, for the U.K. The U.K. formulation was the same as the final formulation, the same as the U.S.

DR. KING: I have a question more related to what I call original sin; that is, when you start to issue cultures and fibroblasts, you start with bovine serum albumin, fetal calf serum, other things.

There was an issue awhile back about the spongiotic encephalitis type things. And so, do we know for sure that the product, the serum that you got is fat-free? Where do you get your source of the fetal calf serum?

DR. NOVAK: All of the manufacturing reagents, and in particular the fetal bovine serum, is from a certified source to be free of any adventitious agents. So that's under control for the raw materials.

DR. KING: I never did find anywhere what was maybe proprietary, what are the actual ingredients when

you start the fibroblast culture. Because, you know, the keratinocytes and other cells will die out with passage, but original sin, if there's something in there that changes their metabolism or surface expression -- so is it proprietary what's in there?

DR. NOVAK: Yes, it is. And I can tell you again that because of the nature of the cultures, they are selected for fibroblasts just by the nature of the course of culture and the media that's been chosen, et cetera.

DR. KING: I understand. I was just trying to find out did you regulate for the antibiotics and other factors.

DR. NOVAK: Pardon me?

DR. KING: Did you regulate what you used for the antibiotics?

DR. NOVAK: Oh, yes.

DR. KING: Okay. I'm just saying you had penicillin first, so you must have put something else in there because it gets contaminated.

DR. NOVAK: The initial culture --

Mr. Maslowski, you want to address that?

We no longer use penicillin. There are antibiotics used earlier in the process that are not maintained through the continuation.

If you want to comment.

DR. MASLOWSKI: I could just share that they're not penicillin-based; they're cephalus sporum-based. They're typical cell culture antibiotics for broad spectrum bacteria and for fungi, but not one of the penicillin.

DR. KING: I was looking for a potential explanation as alluded to for an angio-edema since a lot of those products can be inducing angio-edema.

DR. GERSON: May I just query whether and what characterization there may have been of the final product to show the absence, or the level of absence, of those added materials?

DR. NOVAK: Yes. Again, I'll have Mr. Maslowski answer the question. There has been residual testing that's been performed.

DR. MASLOWSKI: As part of our BLA filing, we presented residual testing on selected reagents that would not have been diluted out by massive amounts of

change over media and we presented those in our final BLA, and we're well within the sub microgram per ml level, some down to nanogram. I think because of the component priority, we did not list each one and their result, but the results were filed with the agency with the final concentrations and the final product.

DR. GERSON: Dr. Olding.

DR. OLDING: First, a question for the FDA. It's my understanding that the pivotal studies were conducted with input from your group, and I'm wondering why a diary was not included as part of those suggestions, or maybe I just don't understand that you don't suggest that, or perhaps I should ask the sponsor the same question. That's my question in general.

DR. WITTEN: Well, I would defer to the sponsor, except to say that we looked at it and we looked at the information that we had. I think at the time perhaps the significance of capturing these early events or how to capture them may not have been totally clear to us, but the sponsor may have something to add to that.

DR. NOVAK: Again, to echo that, in hindsight,

it may have been very useful in fact to have had a diary card, no doubt about that. We did have serial injections and the experience from previous trials with shorter intervals. Again, we opted not to have the diary card. We felt that the safety data collection from the subsequent visits was pretty robust.

Again, as noted by one of the committee members, even upon return, many of the early events that we may have captured had already resolved. So again in hindsight, it would have been helpful, although I think the testimony to the fact that the events that would have occurred had already resolved by the time subjects would have returned.

DR. OLDING: That was really my question for the FDA. Since I didn’t get an opportunity the first time, I have a few more questions to ask the sponsor.

First, for patients who theoretically come back for repeated injections beyond the three, is that going to require additional biopsies or how long do those cultures last; i.e., do they have to have more of the biopsies which in themselves might cause scarring?

DR. NOVAK: Currently, the manufacturing

process actually supports production from the biopsy. The original biopsy will support all three injection regimens for the nasolabial fold injection indication. So that one biopsy does support the therapy as we're proposing it.

DR. OLDING: But if someone comes back later on and wants more?

DR. NOVAK: Currently, the manufacturing process actually can provide even more cells than what's required, and in some occasions -- and in fact we have retained samples and additional samples that are available, but that's not currently the indication. So we wouldn't be treating on a follow-up basis from the original manufacturing process. In the future, again, we have a process that is expandable and has the capability to go beyond the three injection regimen, as well, but that's not the current plan.

DR. OLDING: All right. I want to be sure about the bovine question, which has been brought up a couple of times.

I know that initially people who had been sensitized to bovine products were not included, and I

think you had suggested, at least in the packet of information, that people who were previously bovine-allergic should not be receiving the product.

Does that mean that the bovine products are not completely washed out and theoretically the patient could be allergic? Because if that's the case, that's 3 percent of the population, and then is the test dose appropriate?

DR. NOVAK: The validation study to demonstrate the robustness of the washing procedure, which is again from the cryovial drug substance through washing procedure, the preparation of the injection itself, which is cells suspended in media, not containing the protein or any sort of bovine product -- again the washing procedure has been demonstrated through validation to remove bovine serum components to very low levels. I should also add that the bovine serum again is not a component of our cryopreservation.

DR. OLDING: I only have one more question. This is for Dr. Weiss.

The efficacy rates in the co-primary endpoints

were 33 percent and 19 percent for the two studies by the evaluator, not by the patient.

Could you comment on your -- because it sounds like you have a lot of experience with other injection types, other fillers. Could you comment on your thoughts about having a 66 percent failure rate following an injection at six months?

DR. WEISS: Just to qualify, I think you're referring to the 005 and 006.

DR. OLDING: I am.

DR. WEISS: I wasn't one of the investigators in that trial. But to answer your question, the filler studies we do with the volume fillers, like hyaluronic acid or the J&J product, which is the porcine collagen, they're big volume fillers, and it's a very, very different technique. And so your level of improvement is going to be much greater when you can add more volume here. We're limited for volume, and what we're theoretically trying to do is to stimulate more collagen in the dermis more superficially. So I kind of expect a much lower response rate.

DR. OLDING: If you were going to see a

physician and you had a 66 percent failure rate of a product, would you have that product?

DR. WEISS: Well, I think the failure rate is based on a two point on the scale. I think it's considerably higher with the one point. And I can just go based on the patient satisfaction from the older studies that I participated in, and for the vast majority it was high enough to get satisfaction.

Like everything we do, we tell people it's not going to work 100 percent of the time. We try to give them reasonable expectations. We would explain that this is not a volume filler, that we're working on very superficial wrinkles. But I think that I wouldn't expect that much of a high rate with two point conversion but I think the one point in the scale conversion is satisfactory to me. That's the best way I can answer that.

DR. NOVAK: I'd like to just make an additional comment to that, and Dr. Smith will also comment.

It is a good question. With regards to response rate, what does that mean with regards to

clinical utility or satisfaction of the patient? Again, I'd like to just make the comment that studies were designed as treatment effect studies. We targeted the 40 percent response rate or greater for the treatment group and 20 percent or less in the vehicle group based on early study expectations.

We're held to a two point move on a scale for the evaluator as well as the subject and both sides of the face were actually being evaluated. Now again, if one does look at the data in a slightly different manner, potentially looking at a one point move if one evaluates the subject data, as well, again satisfaction or response, if you will, is also subject to the opinion of the individual being treated, as well, again, what's truly a meaningful response. And, in fact, in other studies for other types of products, as well as in the literature, oftentimes even a one point move on a scale in fact is significant.

I only add that because the robustness that was built into these studies, again, was designed specifically as a treatment effect study as opposed to trying to achieve a study that gave you the optimum

response rate by either of the scales. So again, the design of the study and the fundamental premise was not to get the absolute best result under the best circumstances with this particular design. It was designed as treatment effect, and I hope that helps.

DR. GERSON: Could we move on? Dr. Newburger?

DR. NEWBURGER: Thank you. I have two questions. One, I think would be for FDA, which relates to safety. And that would be actually Dr. Thomas.

My information is a little bit out of date, like about 30 years, but when I was doing cell culture work at the NCI, I recollect that there was a real problem with phage contamination of some cell cultures, and this didn't always reflect in altered morphology of the cells.

Is that still an issue? Is there possibility that there could be a viral infection of the fibroblasts that are being cultured? And, if so, is there some type of probe that could be used to look for viral sequencing?

I ask that as a potential safety question, and

if I’m all wrong, just tell me.

DR. THOMAS: We don’t require a viral test, but the cells are autologous, so presumably they’d be an autologous virus.

DR. NEWBURGER: As a laboratory contaminant, as a laboratory-acquired contaminant, which was a real issue a number of decades ago.

DR. THOMAS: The tests that we used for sterility doesn’t include viruses, no.

DR. NEWBURGER: Thank you.

The second question I have is relating to the sponsor.

The early studies that I read --

DR. THOMAS: Could I make one more comment? Sorry.

The manufacturing facility where it’s manufactured is on the current good manufacturing practices, and so you wouldn’t expect to have a viral contaminant.

DR. NEWBURGER: Thank you.

The other issue was, in the initial studies with Isolagen that were published by Dr. Boss a number

of years prior to these studies, I noticed that there's a real difference in the injection technique. It was made clear that it had to be at the dermal subcu plane plus mid dermis plus high dermis.

Now, is the reason that that has changed to the current injection technique because you actually found in some way that all that was necessary for the effect was to be high on the papillary dermis or was it to avoid the inevitable hematomas and tissue reactions? What is the basis for the change in the injection technique?

DR. NOVAK: Dr. Boss is here and he's available for this question.

DR. BOSS: Thank you. I think you alluded to the point. Unnecessary distribution of the material into the subcu plane was to be avoided, and also the chance of hematoma for the cheaper injection was higher.

So to try to maintain the clinicians or having them avoid going too deeply, it was then stressed and also to inject more superficially. And also in different layers of skin, the depths of the skin or the

thickness of the dermis is different. And, again, it's a very thin dermal area, such as around the lips, and it's very easy to go into the wrong plane and get bleeding and reaction and waste material.

We found that raising a wheal in that level was much more easier for the clinician to see and understand.

DR. GERSON: Dr. Boss, could you identify yourself, tell us a little about yourself?

DR. BOSS: I'm William Boss. With my lab partner, I originally came up with this idea in 1992. I haven't had any affiliation with the company since 2002.

DR. GERSON: Dr. Taylor.

DR. TAYLOR: I have two product questions and two study questions.

With regard to the product, you stated earlier that you subject the final product to flow cytometry. Are there any cells in the final product not stained by the two antibody markers that you use? That's the first question.

The second question is, is the biopsy itself

inspected in any manner for abnormal cells, and have any tumor genicity studies been done with the resulting cells? And then I have two study questions.

DR. NOVAK: With regard to biopsy, there are acceptance criteria. It's a visual examination and there's not extensive characterization of the biopsy itself. However, they are inspected for any abnormal or exogenous contamination, any other kind of characteristics.

With regard to tumor genicity, studies have not been conducted at this time with the injection, reinjection of cells, for example, with the specific attempt to induce tumors. Again, we've relied on the literature and knowledge from other datasets at this point as well as our clinical experience.

DR. TAYLOR: And with regard to the antibody staining?

DR. NOVAK: The antibody stain, again, we have two antibodies that we're using, and during our validation, there was -- and again for proprietary reasons, we won't go into the exact number, but there's not a 100 percent staining.

But with regards to sorting the population -- so for each marker, we've gotten as close as we can to 100 percent of the population and we cannot tell by the way we do the assay whether or not there's any cell that is excluded by one or the other stain or both, if that makes sense.

DR. TAYLOR: So if I can clarify that, what I think I hear you saying is that you don't know what percentage of the final product is not stained by your two antibodies?

DR. NOVAK: We do know by the way the assay is run, but the way the assay is run, we can't tell you if -- John, maybe you want to address this before I go down the -- I apologize.

Mr. Maslowski.

DR. MASLOWSKI: The only part I can mention is that the limited detection of each antibody was established in method validation. So through that limited detection, we know that population has been stained. But like I said, limited detection gives you enough variability where you can't say it's 100 percent.

DR. TAYLOR: When you do fact staining, you can see whether or not there are events that occur outside of your criteria. And the question -- what I'm trying to get at is what percentage of cells are neither of the two that you're talking about?

DR. MASLOWSKI: I think because our limited detections are so tight, it's definitely less than 1 percent because we're dealing with a very small range anyway from 98 to 100.

DR. TAYLOR: So my two study questions, first I guess I have a very simple point of clarification, mild, moderate, severe adverse events; how were those defined? But with regard to that, it seems to me that a preponderance of the adverse event data relate to something that could be kind of grossly classified as increased stress or decreased immune competence or something at the injection site.

There's an incidence of herpes. There's an incidence of cancer. There's an increased event of alopecia. There's a para-psoriasis. There are papules. There's swelling.

So I guess what I'm trying to understand is,

well, whether or not you have any comments on that. Then the second study question is in your integrated data with regard to 7,000 patients, was there any increased numbers with regard to ethnic and race breakdown and adverse events?

DR. SMITH: Stacy Smith again. So the first question was with respect to the injection site reactions and how are those characterized.

In the Pivotal Studies 005 and 006, investigators were asked to use the CTCAE database to categorize those reactions.

DR. TAYLOR: That’s not really the question.

DR. SMITH: Oh, I’m sorry. Go ahead.

DR. TAYLOR: The question is more -- it seems to me that when you aggregate the types of adverse events that were seen at the injection site, you can begin to get some inference that there is an increase in reactions that have to do with immune response or --

DR. SMITH: You’re talking about things like herpes reactivation and so forth?

DR. TAYLOR: Yes.

DR. SMITH: I would actually disagree a little

bit with that. In patients who undergo any kind of facial therapy, be it injection of this product, the dermal filler, resurfacing procedures, chemical peels, et cetera, there's always a concern for activation of things like herpes, reactivation of autoimmune or immune disorders. And I wouldn't consider those specific to any one particular therapy. It's common practice to prophylactically treat patients with antiviral agents before they have these kinds of procedures.

DR. TAYLOR: So the question is how does this compare percentage-wise to those other treatments, filler treatments and other things with regard to the reactivation of these events?

DR. SMITH: There was no formal analysis of, say, published data with respect to herpes reactivation, et cetera, but a good look at the data would suggest that this is well within the realm of what a practicing clinician might expect with a facial injection or facial modifying-type therapy.

DR. GERSON: Dr. Kwak.

DR. KWAK: So this question is for the FDA

clinical efficacy review.

I want to come back to the point I made earlier this morning. and that was, well, with the goal of alleviating my potential concern about the introduction of bias if the study wasn't rigorously blinded.

I'm trying to understand how in a practical level this occurred at the sites. I understand that there was a separate -- the physicians were separate who injected the treatment and who evaluated it. But practically speaking, I'm assuming these are clinical practice sites, so maybe different partners from the same practice, and were some of them sometimes injecting and sometimes evaluating? If so, what kind of safeguards were put in place to make sure they were really operating independently with regard to the evaluation of the individual patients?

DR. SMITH: So the question is regarding the blinding and preservation of the blinding.

You're correct in that the design of the study is that there's an injecting doctor for a given patient and an evaluating doctor for a given patient. The

sponsor required any sites that participated have two doctors, two board-certified dermatologists or other qualified individuals. At some sites, every patient would be injected by one doctor and then every patient would be evaluated by another doctor. At other sites, there was what we call a flip flop where patient A was owned by one doctor for injection and patient B was owned by another doctor for injection. Separate source documents are kept for the injecting doctor and for the evaluating doctor and those are not shared, and physicians are carefully counseled and instructed not to discuss those cases.

This type of study design is actually very common in these kinds of aesthetic therapies where there is potential unblinding from delivering the therapy, just like there would be here.

DR. GERSON: Dr. Woo.

DR. WOO: I have one question about product and then a couple study questions.

The first one is that the product, as I gather, the cells when they’re grown takes about 55 to 60 days, but it actually was only two to three

passages, is that correct?

DR. NOVAK: That's correct.

DR. WOO: Doesn't that seem a little bit long for passage? It takes 30 days for cell passage?

DR. NOVAK: These are primary cell cultures established from biopsy. So it's not unusual to actually have the growth phases such that the passage is actually that low for that long period of time.

DR. WOO: Then questions about the efficacy outcome.

The first one is that what is the concordance level between the responders from the subject's evaluation versus the evaluator's assessments? I mean, the question is whether it's the same individual who's been rated to be responder by both groups or are they discordant.

DR. NOVAK: The only delay is we're looking to see if we actually have the data available. It might be -- this is direct patient to patient concordance. If that slide isn't handy, then we'll need to defer.

So with regards to the correlation of response, this is again a correlation between the

subject and the evaluator assessments. This is for both 005 and 006. As you can see, the IT responders by subject assessment; again, from the original data, it's 57 in the IT group and for the subject assessment 33 in the evaluator, so concordance. And again, I'll look to my colleague.

Mr. Hennegan, can you explain?

So the 54 total IT subjects that could be responded in both, 74 percent responded in both assessments. And I think that probably addresses most of the concordance issue; of the 15 total vehicle subjects, who could have possibly responded in both assessments; 47 did.

I don't know if that addresses the concordance as directly as you'd like.

DR. WOO: So the last column, when you say both, that means the 27 percent of the responders actually is concordant with both assessments and the others are not? Is that what I'm seeing in the 005? I'm just clarifying.

DR. NOVAK: These are the actual numbers of subjects and not the percents. So 27 in the IT group

responded in both the subject and the evaluator, three in the placebo group responded in both subject and evaluator, whereas for 006, 13 responded for both the subject and the evaluator and four for placebo.

DR. WOO: So maybe we could get some more analysis and you can come back to me.

DR. NOVAK: I'd like to do that, if that's possible. We'll break it down in a more meaningful way.

DR. WOO: Thank you. My last question is that I still go back to my original question of the lack of an objective assessment of outcome of the responders. And I share Dr. Newburger's concern that when you have two different trials with very different outcomes, 19 percent versus 30 some percent in terms of responders and so on, and then you have such difference of the outcomes between different trial sites.

The question on my mind is that whether this is -- so if you would look at only those sites that give you lower responders and include statistics on that alone, would that be an effective outcome? And if it is not, then the question really is is the product

really effective? If you take the -- then the effectiveness of the product is really evaluator-dependent or site-dependent. So in my mind, I'm not convinced yet that the product is effective, and I'd like to give the sponsor another opportunity to convince me that I'm wrong.

DR. SMITH: Stacy Smith again. So the concern is a couple of things. One, the tool that's used to measure effectiveness is the scale, and I'll talk a little bit about that, and then the disparity between both the trial sites, those three sites in 006, and the 006 and 005 data.

As a physician who conducts a lot of clinical research studies in dermatology, we are longing for a very objective measure. If you do a blood pressure study, put your arm in the machine, you get a blood pressure number. It's very nice. Such tools simply do not exist in dermatology.

Dr. Weiss told us about a particular camera system, and I've had a number of camera systems and other systems in my office to try and make an objective measure of these kinds of measurements. We've tried

ultrasound. There's silicone impression tools where you make molds of the patient's face or whatever and have those submitted for laser scanning, and none of them validate and none of them are clinically meaningful.

So, unfortunately, we are stuck with what are called photo guides or photo numeric scales. So that's what was used in this trial and that is unfortunately still in dermatology the state of the art.

With respect to the differences between the two studies, it's clear that there were three sites that did not perform very well. The threshold for success here is very high. It's a two point move on a six point scale and it had to occur in both nasolabial folds or nasolabial fold wrinkles. Therefore, that's a very high hurdle to meet. It's not surprising that the efficacy measured that way is quite low. There clearly seems to be some issue with the way some evaluators were implementing this scale.

That being said, my understanding of the statistical analysis that was provided by FDA was that when you take those sites out, there's still efficacy,

and when you do those three underperforming sites separately as a statistical analysis, they are significant and I would ask the FDA to correct me if I've interpreted that wrong.

DR. LEE: Okay. If you take a look at the outcomes of the two co-primary endpoints for three sites versus the remaining sites, the only pair that is now statistically significant would be the efficacy result for the Evaluator Wrinkle Severity Assessment for the three sites alone.

Is that clear? Okay. Thank you.

DR. WOO: I'm still kind of skeptical in a sense. If you look at only those three sites, the 6100, the 6300, and 6600; if I add them all up, there are four responders out of 61 individuals from the IT, and from the vehicle, there are two responders out of 50 something.

So if you look at those three sites alone, then this thing is -- I would say if there is any effect, it's got to be very minimal. So then you have very -- different sites can give you such diverse results. It really gives me a lot of doubt in terms of

whether this treatment is really effective.

DR. WEISS: I'm here today because I've seen patients long term. I sincerely believe that this would be a good part of the armamentarium and I can understand and agree with your analysis with the sites and I certainly have, you know, similar concerns looking at the data. But the fact is my experience has been overall excellent, and patients keep asking me when is this going to be available. And so I just wanted to add that. But there's no one who can argue with the numbers that are presented.

DR. GERSON: Thank you.

Dr. Chappell.

DR. CHAPPELL: Yes, I had two questions, but one was specific to Dr. Lee about this issue.

I like your presentation and particularly slide 15, you address this issue exactly by looking at the vehicle and IT rates separately for each site, and you showed that two of the three sites was zero vehicle rates, also at very low IT rates. And it's not just true for those who have zero vehicle rates. During the discussion, I actually plotted them on my laptop and

you can -- well, you can't, but I can see a very strong trend. Those with high vehicle rates have high IT rates. Medium vehicle rates tend to have medium IT rates. So they're very strongly correlated. There seems to be an effect. IT is higher than vehicle, but there's a very, very strong center effect.

Now, these were evaluator wrinkle severity assessments. So that means, if there's a strong side effect, the patients could be different between sites or the treatment could be different between sites and the vehicle could have some effect, and it could be given better in some sites and worse in others, or the evaluators could be different between sites. The sites are different, but it's hard to tell.

Now, you can eliminate the evaluator effect by doing exactly what you did, except for looking at success rates in patients, patient self-assessments between sites.

So if you saw a high correlation between IT and vehicle rates among patient assessments between sites, then you'd know either the patients are different somehow or the treatments are different and

we should emphasize training.

So do you know, did you do that kind of table for patient assessments?

DR. LEE: Correct me if I'm wrong. I believe you are saying about Study 6, and to look at the three sites versus the remaining sites, is that correct or not?

DR. CHAPPELL: Right. But there's also a zero percent vehicle success rate in Study 5.

DR. LEE: Right. Study 5, I had not done that. Study 6, I did that for the three sites specifically compared to the remaining sites in the same study. So the only pair not statistically significant is the one of the Evaluator Wrinkle Severity Assessment endpoint for the three sites --

DR. CHAPPELL: But I was talking about the patient self-assessment.

DR. LEE: Right. Patients, that one is statistically significant for the three sites as well as for the remaining sites.

DR. CHAPPELL: But is there a difference between -- so there seems to be an effect?

DR. LEE: There's effect in the subject.

DR. CHAPPELL: I'm not asking about the effect of the treatment. I'm asking about the effect of the sites and what it's due to. Right now by showing that for the evaluator assessments, sites with low rates for vehicles also have low rates for IT. That says there's something different about the patients, the treatment or the evaluators.

DR. LEE: But when we look at the patient characteristic for the three sites compared to the remaining sites, we could not find out the outstanding issue for those patient baselines.

DR. CHAPPELL: Okay. Then there's something different about the treatment or the evaluators.

Now, if you look at that same kind of table just for patient assessments, --

DR. LEE: Right. It's on the same slide, on the right-hand side.

DR. CHAPPELL: Slide 17. Yes, but separated by site. But if you had the equivalent of slide 15 for for patient assessments, --

DR. LEE: Oh, okay. I understand what you

mean.

DR. CHAPPELL: -- then you could see if there was -- there's a strong correlation between those percentages in the middle row and the percentages on the right row. That's all I'm saying, that there's something similar about the results for treatment and control when it's evaluated by the evaluators. But I'm wondering if the same is true if it's evaluated by the patients.

DR. LEE: That analysis I have not done yet.

DR. CHAPPELL: Okay. Because then if that were true -- because I like this analysis, and if it were similar -- if the patients seemed to be more satisfied where they are here for both vehicle and IT, then you could say, aha, the treatment varies, which might indicate that you would want better training.

DR. LEE: Well, I can make a comment about the subject assessment endpoint. If you will take a look at by study size for the IT and the vehicle, even though this is specifically for Evaluator Wrinkle Severity Assessment, for that I will comment that there was no specifically, a particularly lower success rate

for the IT treatment in the Subject Wrinkle Assessment, because there was a pooling analysis that's conducted and it's based on the Breslow-Day test because Cochran-Mantel-Haenszel was stratifying by slide, and it's got to produce the Breslow-Day Test. But again, the p value is really not a significant p value. But again, study was not designed for that purpose. It's really difficult to make a judgment about that.

DR. CHAPPELL: When you say it's not significant, is it just for the patients or is the patient evaluator --

DR. LEE: For all evaluator and the subject.

DR. CHAPPELL: Okay. Thanks.

DR. GERSON: Dr. Snyder and then Dr. Dubinett.

DR. SNYDER: I guess I have two questions. One just came up in listening to this discussion.

Correct me if I'm wrong. Aren't the evaluators' assessments at six months done with photographs, is that correct? Am I correct on that?

They're not? Because if they're done with photographs and there's a concern about evaluator bias, can't the photos from one center simply be sent to the

evaluators at another center to see if there's concordance in evaluating the exact same data?

DR. NOVAK: They weren't done with photos. The primary endpoint was a live assessment.

DR. SNYDER: One of them says here, though, that at six months, the evaluator improvement assessment is based on photos.

DR. NOVAK: That's right. That's a secondary endpoint.

DR. SNYDER: Well, I mean, wouldn't one way to reconcile this as to whether there's evaluator bias between centers is to simply send the photos to assessors at another center and see if their assessments are the same for the exact same photos and then you can get a sense as to whether it's investigator bias or evaluator bias or not, or whether there really is a difference between centers? That's just a point.

It sounds like it would be a very, very simple way to reconcile this simply by -- it's objective criteria to an extent in that everybody's looking at the same photos.

That wasn’t the main question that I wanted to ask, though. That was just something that occurred to me during the discussion.

I just wanted to revisit one question that I had earlier, and maybe this might actually be best addressed to Dr. Boss who did the preclinical work.

As someone who does a lot of transplants, I’m always interested in what the fate of the cells are in vivo, and I’m just wondering whether somebody could just give me some information as to what happens to the cells after they’ve been transplanted.

Do they stay quiescent? Do they continue to divide? Do they die? And if they’re still around, can they be induced to redivide by an injury, by an infection, or just over time?

DR. BOSS: Thank you. In my preclinical trials or early experience, I did some biopsies of non-treated risk to test those areas and areas that were dosed, and we might have available an example of one of those showing increased thickness of the dermis.

Although these were not clinical trials per se, clinical experience in -- for example, some

patients, one patient had a very high level of intrathecal steroids injected for a bad back about two years afterwards. And she came back to me and had noticed that she clinical effect had gone away.

Having looked at her and evaluated her, I said, “Well, let’s wait for awhile and see what happens.” We gave her ascorbyl palmitate cream several weeks later after the effect of that intrathecal steroid would have been resolved or gone away and she re-responded. In fact, I still see her today. I think she may have forwarded you some of her own experiences in some of the transmissions that you’ve gotten or solicited from patients.

A number of other patients that we’ve seen have also seemed to respond better, you know, several years later, to topical creams or, say, micro-dermabrasions, things like this; although I don’t want to make that assertion. It’s just my own clinical impressions since you asked me for that.

So I have indication in my patient base of clinical activity and a large number of my patients still come back, even 10, 15, 20 years later, not 20

but 10 -- seems like 100 years later, but they still come back and are very positive about their experience with the treated areas and are continually asking me when it will be available for new injections.

DR. GERSON: Dr. Dubinett.

DR. DUBINETT: One of the questions I had did relate back to the question of the site to site variability. And I think, Dr. Smith, you had called these three centers underperforming, and I guess that implies that we have knowledge of something about their performance in terms of the criteria.

DR. SMITH: No, that's probably just using a poor terminology. I mean, we're just comparing them to the --

DR. DUBINETT: Okay. I think one of the interesting things is it's half the centers, is that right? So 006 had six centers and three of the centers had either 5 or 10 percent response by the evaluators and the others had higher.

So it was my understanding that -- is there some specific criteria that's been found in those three centers versus the other three centers to --

DR. SMITH: No, that's what this debate is all about. It's clear that looking at the center by center efficacy data, that those three centers have lower efficacy compared to the other centers in 006 compared to the 005 centers.

DR. DUBINETT: So underperformance then would not be a word to characterize those three centers?

DR. SMITH: Only if you're comparing them -- I guess --

DR. DUBINETT: Underperforming. In other words, there might -- what I was getting at is that there might be some criteria to call the other three underperforming.

DR. SMITH: Oh, you mean they might over-represent the efficacy? Is that what you're saying?

DR. DUBINETT: Yes. So, in other words, there's no criteria for underperformance in these six centers that we know of?

DR. SMITH: No. They just simply -- the data is different at those centers and that's all I know.

DR. DUBINETT: Okay. And given that, since one could consider the 006 to be a center of

excellence, are there plans to have in the center of excellence program that will happen, some correction of that, so 50 percent are not different from the others?

DR. SMITH: Well, I would imagine that -- well, I'll let you discuss centers of excellence.

DR. NOVAK: I think the short answer is yes. Obviously, we have trained physicians that are out there with regards to the statistical results from those sites. Obviously, they are quite different than the majority of the sites that were included in these two trials.

So the answer is yes. Everyone through the centers of excellence will undergo, again, training and we certainly will be doing some post-evaluation of some of the data we've not yet gotten to, even continuing to query what might be the underlying reason for, in fact, the scores being so different at these three sites on the evaluator scale.

Again, to date, we have looked at as many correlations as we can and we just can't come up with a reasonable suggestion, other than, again, the particular utility of the scale.

I can say this. I'll stop there, actually.

DR. DUBINETT: So my other question related to the laboratory, and that is under the culture conditions that you have, do you have knowledge of the proteins that are produced by the fibroblasts, such as TGF beta, fibroblast growth factor, IL6? Is any of that known?

DR. NOVAK: That work has not yet been done.

DR. GERSON: Dr. Rao.

DR. RAO: I had two issues and both of them are questions for the FDA, really.

One of them is related to manufacturing the cells. You know, there were questions raised about serum and residue of protein and we don't quite know what the test is to evaluate it, but presumably the FDA's familiar with the fact that serum proteins can be taken up by cells and the glycol proteins can still be active and can persist in cells. So presumably there's some tests and hopefully the FDA has made sure about that.

The second issue with that was this proprietary marker, and I think, as Doris and others

alluded to, hopefully the proprietary marker has been tested in some system to show it's specific for fibroblasts in this sort of mixed culture and doesn't label, say, mass cells and it doesn't label the endothelial cells, or anything else that's reasonable contamination of that population, because if it is, then that 90 percent number will contain a mixed population of cells. And presumably, since we don't know what the proprietary marker is, the FDA has been satisfied on that score.

The third thing was that we talk about a dose range which is quite large, between 10 to 20 million, but it's all at the level of the cells in a culture dish.

Presumably we need to be concerned about what actually goes into the patient, and there maybe we have some kind of study which says what the residual cells are, what is the residue of the cell number that's present in the injection as a critical criterion in terms of determining what's happened and what's gone in there. So those are sort of manufacturing-related issues for me.

The other thing was on the clinical study side. You know, of all the side effects that were reported, there are really three which are relatively unique to cells and possible proliferation of cells, and that's there was some thickening, there was nodule formation, there was a report of fibroblast overgrowth in that case in one of those patients.

We don't know what the cause of that is. That could be secondary. So presumably there's either data there saying that equivalent fillers and so on caused similar effects in the same range or if this is unique to cells, then perhaps some correlation with proliferation rates of cells because we know that long-term culture of cells can cause a change.

I just did a ballpark calculation with Dr. Snyder here. Presumably starting off with a sample which is 100,000 cells or so from the biopsy and you're going up to 10 to the power 8, right, because you're going to 40 million cells or so and you have some residue of cells left behind. That means at least 12 population doublings, maybe 15.

For MSC and other cell populations that have

come up here, we've been worried about more than 10 or 12 population doublings. So it may be something to keep in mind, as well. I don't have the data because that's not been presented, so we don't know, but that's why the questions are to the FDA.

DR. THOMAS: Thank you for all those comments. I can't really say too much, but the residual levels that are in the final product are acceptable to us.

DR. GERSON: Would the sponsor like to comment on that before we move on?

Ms. Rue.

MS. RUE: I have one question for the FDA and a comment. And I probably missed it in the discussion that we did on the safety results, but when we were talking about the commercial experience and we talked about the U.S. and the U.K. population, which is about 9,000, and you did a retrospective chart review, I didn't get actually what percentage of those 9,000 was looked at as far as the safety issues.

But the comment I have, as the consumer representative, is that not to discount the physician's evaluations of the positive effects, but if the client

that's receiving this procedure only because they're not happy with the experience is not happy with the results, this product's not going to sell and people aren't going to come back.

So one of the focuses, I think, besides the physician, is, more importantly, is if the patient perceived that they had positive. And that's just a comment. But I think it will be proved that it is safe, that is the biggest concern.

So if the FDA could answer?

DR. WITTEN: Well, just to clarify about the retrospective review and the U.K. experience, that's based on what the sponsor provided us and the retrospective review that they performed. In other words, they give us data that they look at. So I'm going to refer that question to the sponsor in terms of telling us exactly what that retrospective review was.

MS. RUE: Thank you.

DR. NOVAK: For the U.K. data, it was a result of querying the spontaneous reporting data that we received. So that was not a review of case report forms; they don't exist. Charts do exist, but again it

was in the U.K. So this was a query of the data or the actual reporting that came to the company spontaneously. So it's a small subset of the patients treated.

MS. RUE: Any idea what percentage of them?

DR. NOVAK: Well, if one looks at 6,000 patients treated in the U.K. and the data we presented represents a handful of those, we only received reports that would indicate there might have been a problem. We didn't receive, for example, data where there were no problems. So all I can address is those are the numbers we received.

DR. GERSON: Maybe I could just acknowledge that the subgroup analysis by the FDA raised an issue of efficacy in patients over the age of 65 and I'd like to offer the sponsor an opportunity to provide us with a perspective on that analysis and perhaps intentions and their understanding of the use of this product in their subject patients or perhaps prospectively in individuals over the age of 65.

DR. NOVAK: Again, I'll first address the issue with regards to the current plan. The current

plan is not to necessarily exclude anyone over 65 years of age. That's based on a couple of factors. One, we have experience and we can manufacture the product. As far as the outcome measures, we believe the numbers are, again, still a little bit too small to exclude the possibility of a clinical benefit for these individuals.

Our plan is to go forward and again collect data, and that was part of the presentation on the clinical support center, that one of the things we want to do is, in fact, collect data on the demographics as we see this product expanded into, again, a larger number of the older population. So at this time we don't have any intention to exclude those, but we do have intentions to collect data and be more careful, more robust, if you will, in the analysis with larger numbers.

As far as the clinical experience, I don't know if you need any additional commentary on why we might believe that there could potentially be a lower effect. I would refer to a clinician, but at this point I feel the numbers are small.

DR. GERSON: Dr. Drake.

DR. DRAKE: I brought up the issue of biopsies before and the reason is because I'm not sure that anybody knows what you're looking at. And so my question is, you know, there's a lot of difference between repair and healing and remodeling. There's all different ways the skin looks different, and we don't know why the skin is looking different here. And it is possible theoretically -- I mean, I'm just thinking outside the box. But it's possible that instead of getting a nice normal healthy reaction to this treatment, are we in fact getting scarring from collagen bundling and getting a small scar there which plumps up the thing and that's a totally different animal than a normal response. Nobody's mentioned what's happening to elastin. I mean, I'd like to know if we're seeing any elastin on this after the injection.

So there are a lot of questions there, and it's a well-agreed-upon concept that the elderly tend not to scar as well as younger people. They just don't have the mechanisms to form nasty scars. And so maybe

we're looking at scars in the younger people and the elderly are not forming the same scars as the younger people. I mean, I think that I don't know what I'm looking at here and I want to know if the company has any notion of what I'm actually looking at, besides plumping of the wrinkle.

DR. NOVAK: Again, we don't have any direct evidence, but my colleague from Vanderbilt did present data, at least in an animal model, not our data. Again, what we presume is occurring is that the cells in fact are moving into that space and residing for some period of time and participating in the elaboration of extracellular matrix. What that looks like -- yes?

DR. DRAKE: Is that with your product?

DR. NOVAK: It is not with our product.

DR. DRAKE: That's the whole point. That's the whole point.

DR. GERSON: Further response to the question.

Dr. Newburger.

DR. NEWBURGER: My comment was that of Dr. Drake, do we know that we're not dealing with

controlled scar production as is the case with some of the injectable fillers that are devices where it is controlled scar and it’s not normal collagen.

DR. GERSON: Dr. King.

DR. KING: I guess I have two comments and then one question.

The first comment is you learn from business. If you have a big business like McDonald’s, you have to make sure that they keep the franchise, you have to keep the doors clean, the burgers cooked, you know. So you’re going to have to pay attention to that, both from the standpoint of satisfied clients but also from the standpoint are you going to be put in a position that somebody says you’re excluding us and, you know, you’re controlling the product.

So that’s been an issue in a place called Nashville where they have a lot of hospital corporation of America kind of operation. That’s a big deal.

The other comment is really related to what you talk about with issues. When you’re over 65, like I am, you get to the issue of are your tissues still working or are they just less efficient. And I think

you get to that in a site- and person-specific manner.

When I just saw Jack LaLanne at 95 out in California doing all kinds of things, I'm reminded that people don't age the same and so it gets down to the question very simply to me, are you injecting cells that have been rejuvenated because they took a vacation in tissue culture and got new products going there, and is it a question of volume of cells, which is a whole bunch of old people can make a big noise if there are enough of them; so if you have noise, the increase in the amount of growth factors, nutrients, and so forth. And I would like to know about elastin.

So my question comes back to the same thing that's being repeated here; what are we looking at? What products are being delivered? Is this simply a volume effect or is this scarring or something else that's not been evaluated?

I go by as a dermatologist if it works, it works, you know, but on the other hand, we're talking about safety for people 10 years down, which is why I asked about the bovine serum and so forth. So if you've got clinical issues out of the way, at the end

of the day does it work and is it safe.

DR. GERSON: Seeing no other questions and comments to be raised, and we're a little bit after 1 o'clock, thank you all for the questions, for the presentations.

We will adjourn and come back at 2 o'clock for the formal question period.

Thank you.

(Whereupon, a lunch recess is taken at 1:10 p.m.)

DR. GERSON: I'd like to go ahead and get started.

We have a series of six questions, two require a vote by the committee, for discussion this afternoon. Each will be led off by a committee member, and then if the committee members would indulge me, what I might suggest is that we just get a sense of perspective from every member of the committee by a brief tour-around.

If you would like to pass on the specific question, please feel free to do so, but I want to make sure that we have a chance to have everybody heard. We'll spend about half of our afternoon on the first four questions so we have plenty of time to make sure that we get to the questions that require a vote in the latter part of the afternoon.

Before we begin, I'd like to ask, just for a point of clarification for the record, Dr. Novak to give us some follow-up from a point of discussion this morning.

DR. NOVAK: Thank you for just an opportunity for clarification.

The question came up whether or not there was

a pending lawsuit. The current CEO of the company, Declan Daly, actually indicated in fact there's not, but we committed to checking to see if there was something, again, that we needed to tend to and inform the committee of. And basically, there is no current class action lawsuit.

The case number that was referenced in the public letter that was referred to earlier today was a lawsuit, a class action lawsuit initiated by investors and that was started back in August of 2005. It went through mediation and it was settled and closed in March 24th, 2009. So in fact there are no pending outstanding lawsuits.

DR. GERSON: Thank you.

If we could have posted the first question? Terrific. I'll do my best to read through this, if I could.

So the first question to the committee relates to tumor genicity. If approved, IT would be the first cellular product for this indication and the first fibroblast product that is an injectable cell suspension. Uncontrolled cell growth anti-tumor

formation could be potential risks of cultured cell fibroblasts due to their proliferative nature.

In addition, there is a theoretical risk of the post-auricular biopsy transferring abnormal or malignant cells that may not be detected in the quality controls of the product manufacturing.

Long-term follow-up data are limited. One case of basal cell cancer occurred near the site of injection. However, the relationship of IT to this case cannot be assessed.

Based on the manufacturing and clinical data presented and your knowledge of the literature, please discuss any safety concerns relevant to tumor formation and the potential for longer-term, beyond 12 months, risks of this product.

If you believe there is potential risk, please discuss the basis of your opinion and your recommendations to discuss this risk.

I would like to ask Dr. King to help us frame this question.

DR. KING: Thank you very much, Mr. Chairman. I'll try to keep this brief and mostly to have the time

for discussion.

As mentioned, the IT/AT product is injectable and it's autologous. And so, injecting autologous type of fibroblasts is not the same as a dermatologist, plastic surgeon, drawing out fat cells and then checking them without culture. So that's a different kind of presentation.

In general, we don't worry about fibroblasts being particularly reactive because they lack the HLA Class II antigens necessary for antigen presentation and serial passage diminishes the antigen-presenting cells. So there may be a small number of them in the final product, but I doubt it being very significant.

Inducing granulomas and other potential areas of tumor formation, by tumor doesn't necessarily mean cancer, so you can induce tumors and they not necessarily be malignant. So I think unless the culture mechanisms and the proprietary products induce something, whether it's a virus or some other type of long-term promoting effect, it'd be unlikely that these would produce cancers.

Selection of the donor's site is important

because, as a pathologist and a dermatologist, behind the ear can still have cancers and even have melanomas in that area, too. So the question is whether or not anything that they're doing that gives a person back there autologous fibroblasts to produce cancer seems unlikely, unless the selection site is going to be carrying something across that would do that.

In general, we try to grow basal cell carcinomas in culture and probably lost at least one grant because we couldn't do that consistently. So from my perspective, long-term problems would be simply a matter of the manufacturer and incidental effect of a biopsying site where there's some form of malignancy, which could even be fibroblastic because there are fibro sarcomas.

So I'll leave it there.

DR. GERSON: Why don't we just move around the table with a brief discussion? I'll start with Dr. Allen.

DR. ALLEN: I don't really see a huge issue. I mean, the bottom line is autologous. So as has been said, unless there's something about the in vitro

passage that increases the risk of it, the reality is that if the patient's got tumor cells in that biopsy specimen, the patient's going to get a tumor behind his or her ear anyway which will be managed.

So unless there's something that's going to promote that and there's obviously concerns about that; that said, any time we put cells in that have been proliferating outside the body -- and there's always a potential. So I don't think it obviates the need for long-term follow-up.

We really don't have that. Yes, there are 7,000 patients out there, but we really don't have good tracking on them. One imagines if there were tumors, somebody would have said something and we would have heard about it, but I think there's still a requirement for long-term tracking well beyond 12. I don't consider 12 months an adequate period to determine the answer to this question, but I'm not overly concerned.

DR. DRAKE: I agree with them. I have nothing to add.

DR. CHAPPELL: No comment.

DR. NEWBURGER: I wonder if it would be

possible to get perhaps a larger biopsy, 4 millimeter biopsy, and then take a little bit of a portion of it for histologic analysis. There are 10 to 12 doublings in the cell culture. Squamous cell carcinoma does culture quite well, and I'm concerned about that.

The other issue that I have, and I don't know if I could mention this, I don't know what control mechanism there is for the fibroblasts that are being implanted, if in fact they are producing collagen on an ongoing basis, what the signal is for them to turn off. And since it's a short-term study -- I mean, do we know that a benign tumor won't develop down the line?

DR. GERSON: Could we maybe just have -- maybe we'll keep going around the room and remember, if I could, this question and have one of the folks, I suspect from this side, answer the question of in vitro culture predictors perhaps.

MS. RUE: I don't have anything further to add.

DR. WOO: I don't have any specific questions right now, but I would participate in the follow-up discussion when I hear some more.

DR. DUBINETT: So I think with the amount we don't know about these cells and what they're producing, that I think the issue of tumor genicity in my mind is largely unknown for the following reasons.

Fibroblasts are well known to be the source of both fibrogenic proteins, such as TGF beta, angiogenic factors, and proteins that, when, as part of the tumor micro-environment, there's a rich literature to document that they both promote the tumor growth and have an interplay with and are important for tumor genicity.

The products that these fibroblasts might make in regard to tumor growth decreases in cell-mediated immunity are unknown, and under the culture conditions, we don't know what they're making. So I think some of the things that Dr. Taylor mentioned earlier in terms of regulation of cell-mediated immune responses bring to mind that these may be making large amounts of TGF beta or TGF beta family proteins and I think that that would be important to know in order to gauge the tumor genicity.

In addition, the morphologic assessment of

fibroblasts in culture is very difficult to discern the difference between a fibroblast and an epithelial cell that's undergone epithelial mesenchymal transformation that would occur in early stages of carcinogenesis.

So I think there's several questions in my mind that at least raise a concern for this, and I think that there are many unknowns in terms of the characterization of the cells grown under these culture conditions, particularly in terms of long-term follow-up for individual patients.

DR. GERSON: Dr. Snyder.

DR. SNYDER: I certainly kind of indicated before that as a scientist, I certainly would love to know what the fate of those cells are after having been transplanted. I mean, we don't even know if the cells persist after they've been injected, so we don't even know if they're hanging around. I think there's a very good chance that they may not survive for more than a few weeks. So I think there are ways to try to screen the pre-implantation population. At a most simple level, one could simply do karyotypes on those cells and perhaps even screen for other markers.

Having said all that, it's a fairly benign population. It's being implanted into a site that is exceptionally visible, very accessible. With follow-up, if there's a bad outcome, one can remove it. And we've never seen anything directly related to fibroblast proliferation.

I wonder what would happen if in fact a patient received steroids or an injury or an infection, but it's not been seen. And as far as we know, even the patients that were not part of the studies, it probably has not been reported.

So on balance, I would say it's a self-selected population with cells implanted in an exceptionally visible and accessible area. So I think it's probably okay. I'm predisposed to let it go.

DR. GERSON: Dr. Rao.

DR. RAO: I'd just like to concur with Dr. King and Dr. Allen, that, in general, I don't feel taking the biopsy or the history of the cell that's coming from and being transplanted in an autologous setting is high risk in terms of tumor genicity, et cetera, even if it's secreting a large amount or

additional growth factor, given the size and amount of the cells that have been put in.

My only concern, which I sort of raised a little bit earlier, was the cells and their frequency of transforming in culture, which is dependent on the number of passages and it's true for all cells, including fibroblasts. With fibroblasts, there's a little bit more of a concern simply because of the data that we have from growing mouse fibroblasts in culture. Mouse fibroblasts readily transform. We don't know whether that's the equivalent with human cells, but we do know that that's true for mouse cells. And one needs to test that to make sure because there's no morphological criteria which allows you to say that this is a transformed cell as opposed to not being a transformed cell. And either a limitation in the total number of passages, you keep a cell in culture because there's a time period that's been defined by academic literature on what it takes to acquire and select for a transformed cell, or some other mechanism of testing might be something to keep in mind.

DR. GERSON: Dr. Olding.

DR. OLDING: I've nothing to add.

DR. KWAK: I have nothing to add.

DR. GERSON: Dr. Burke.

DR. BURKE: Yes, I agree with everything that has been said, but I just wanted to point out that there are possible markers. I mean, we know that in actinic keratoses and even more in squamous cell carcinomas that you can look very easily at P16 and P53. So there are markers that could very easily be screened, and this could be something that could be done as the initial test of the fibroblasts that are given.

Again, it's so important to see histologically what happens in humans. I mean, it's just very possible to implant these things behind the ear retroauricularly and do sequential biopsies, look at the types of collagen that are secreted, if there's elastic tissue, and see if the cells are just a filler that is remodeled or if the cells are really viable and synthesizing. And these are all relatively easy and accessible and could be done very easily. So I think that's important.

But having said all of that, it's unlikely that you would be transporting tumor tissue. At least it's autologous tissue, it's retroauricular and having had all of these caveats, it probably is safe, but there are ways to make it 95 percent safe to 99 percent safe.

DR. GERSON: Thank you.

DR. TAYLOR: Again, I concur with everything that's been said, with the addition of perhaps markers like P21. We know that fibroblasts have a very strong influence on tumor genicity and tumor cell proliferation and can impact the migratory capacity of tumor cells. And I think it's critical to recognize that and look for some of the early markers.

The other issue, with all the autologous cell caveats being made, I think the cells are probably reasonably safe, but we have not discussed adventissual agents and in fact have been told that the cells are in the presence of serum for a sustained period of time. There's no karyotype analysis. No adventissual agents are screened. No viral adventissual agents are screened, and we really don't know that there's no

transformation of the cells. So I have some concern about how to know at this point whether or not there's any change in the cell phenotype prior to implantation.

DR. KING: I just want to listen to what everybody's said. It's reminiscent of what happens in Vegas may not stay in Vegas.

So the issue here to me is, is it going to be transformed or not, and given we don't know the proprietary type of what's going on, what I'm hearing is that we buy it from reputable sources and so that's what gets you in trouble in Las Vegas. So I'm not sure about we know for sure. I'm not worried about autologous fibroblasts per se, but you put them in culture and then manipulate them, long term in the selected individuals can cause a problem.

So I think it's relatively safe and yet when it happens to you as a bad outcome, it's 100 percent. So I think that's just the nature of clinical dermatology.

DR. GERSON: Maybe I could comment and then open it up for other questions.

I would have these concerns. In general, I

actually completely agree with Dr. Snyder, that this is a visible site and therefore can be assessed daily by the patient let alone a physician.

I would be a little bit concerned in the broader application of individuals with predisposition to transformation because of a genetic inheritance of a cancer family syndrome, whether it be a BRCA1, P53. There are a whole bunch of others and many others that we'll come to know more.

The second population who may be more prone to actually receiving this therapy would be heavy smokers who have, I think, a higher incidence of wrinkles and that population may very well have predisposed molecular events.

The other item that I would query back to the sponsor is we learned that a proportion, a small proportion of the entered patients didn't receive the cells and we were told qualitatively that they were culture failures. We didn't hear anything about whether or not any of those failures could conceivably have been or were documented to have been transformational events.

DR. NOVAK: In fact, none of those discontinuations of culture had anything to do with the transformation phenotype or any other concerns about the quality of the cells. Discontinuation of manufacture had to do with the ability to grow the appropriate number of cells in virtually all cases.

DR. GERSON: Are there other comments on this topic? Could I ask the FDA whether there's other aspects of this that we would like to discuss?

DR. WITTEN: No. Thank you.

DR. GERSON: We'll move on to the second question, if we could have that posted. Thank you.

Race and ethnicity, an increase in safety events in non-Caucasian subjects, and the trial was not observed. However, the study size was small. Please discuss whether or not the data in the trial and your knowledge of the literature suggests that this product has the potential for causing risks, such as hypertrophic scarring and keloid formation or abnormal pigmentation, in the non-Caucasian population. If you believe there is a potential increased risk, please provide your suggestions of how to minimize these

adverse events.

We have asked Dr. Burke to help lead off the discussion.

DR. BURKE: Thank you. First of all, we have heard today that there is an underrepresentation of the non-Caucasian population and we know that blacks form more keloids by far and only 1 percent of the patients studied or presented were black and 10 percent Hispanics. So this clearly needs to be looked at.

We also realized that we don’t know exactly what a 100 percent of the cells are. We presume from the markers that 98 percent of them are fibroblasts and most of the other 2 percent are presumed from markers to be keratinocytes, but in fact there may be mass cells in that population. And we know that keloid scars have more activity of the mass cells that are in fact upregulated in keloid scars. We also know that in keloid scars, there is high expression of transforming growth factors beta-1 and beta-2, and we haven’t looked at what happens in culture with TGF beta-1 and beta-2.

So these are things that might increase scar formation, and, of course, most importantly, which

we've repeatedly said, we don't know the fate of these cells in vivo. We don't know if they're acting as cells, whether they themselves are remaining viable, if they are proliferating and, third, if they're producing Collagen 1, Collagen 2 or elastic tissue or something else, or are they only there as something that stimulates further synthesis as in a wound-healing situation.

So I just want to point out that there is an opportunity for long-term follow-up. If somehow we could have learned about the patients treated in the '90s in the United States and the early 2000s in the U.K. and Australia and New Zealand, perhaps somehow we could find, especially the black populations, and see if there was any incidence of scars.

So I think there are lots of open-ended questions and a study that was just done and followed for six months, we might not see the keloid because keloids can form slowly and progress after that time period. So these are all questions in my mind and I open it to discussion from the other participants.

DR. GERSON: Thank you. We'll go

counterclockwise this way this time so we don't get old from hearing from folks.

Dr. Kwak.

DR. KWAK: I agree. The number of experience in non-Caucasian subjects is extremely limited at this point and I would just defer to Dr. Burke, to her comments and the other dermatologists on the panel about the need for vigilant long-term follow-up in this population.

DR. OLDING: As was presented by the sponsor, it does represent an adequate amount of patients who normally seek cosmetic treatments, percentage-wise. But in one of the studies, and I don't recall which one it was, they did show a better response in African American population. If that's the case, since we don't know what actually the mechanism of action is, if the mechanism of action is scarring, then one would expect to have a little bit better response in African Americans. So I certainly am concerned about that and enough that I would like to see a larger representation.

DR. GERSON: Dr. Rao.

DR. RAO: Just looking at the question specifically, I don't think that there's any data to say that there's potential increased risk in treating other classes of patients, non-Caucasian patients. There's not enough data.

DR. SNYDER: I agree with everything Dr. Burke said. I think it would be interesting to either retrospectively or proactively include some more non-Caucasian patients in looking at that.

DR. DUBINETT: I agree with what's been said by Dr. Burke and have nothing to add.

DR. WOO: I concur.

MS. RUE: I have nothing to add.

DR. NEWBURGER: I would like to recollect that in one of the studies, there was one subject who had persistent firmness in the nasolabial fold, and perhaps that person is a keloid former but that did persist for the duration of the study.

Also, there was the case reported in U.K. where there was a nodular or fibrous overgrowth at the site of the scar. And, in fact, all of the biological factors that have been mentioned may be quite relevant

in such a situation.

Lastly, the two individuals who showed post-inflammatory hyperpigmentation, which admittedly was of short duration, who were identified as non-Caucasian, this is certainly not unusual, but the earlier reports showed that the skin was pre-treated with both a retinoid and Vitamin C, and both of these are very helpful in preventing post-inflammatory hyper-pigmentation in general. Some people use also a topical hydroquinone. So I don't think that that's a major -- the pigmentation, I don't think is an issue. It can be addressed.

DR. GERSON: Dr. Chappell.

DR. CHAPPELL: I also don't see the data. There's 26, by one count, non-minority -- sorry; 26 minorities, if you exclude others, out of 210 patients in the pivotal studies. There don't seem to be an excess of toxicities, but we can't tell. So I would say I shouldn't abstain, but I wish there was a button for I don't know.

DR. DRAKE: I have nothing to add.

DR. ALLEN: I have nothing to add.

DR. GERSON: I would only comment that it doesn't appear to me that we have a reason for concern, except for a small sample size, and the best solution to that is increase the sample size through a prospective collection of data.

DR. KING: I guess I have a simple concern. It's called Pandora's box. If it gets FDA approved, it's going to be out there and what pressures are going to be to find out the numbers. So if you're inducing in some places a mini scar, then my experience with persons of color, that you get hyperpigmentation, whether or not it persists or not, is you get inflammation, you get everything from vitiligo to hyperpigmentation.

So I'd just like to say if we do this, there has to be some caveat that there's going to be some population that will document what seems to be true in white women between 40 and 60 is true for all other ethnic groups.

DR. TAYLOR: I concur with Dr. King. I think the data are not in and we need strong follow-up and reporting.

DR. BURKE: So in conclusion, I think that everyone agrees that there was a relatively limited population of non-Caucasians, although there didn't seem to be evidence, except in one patient, of nodular formation.

I think that it's obviously important to have vigilant follow-up, long-term follow-up, and we all still want to know the in vivo fate of the cells.

Dr. Newburger mentioned that we can in fact treat post-inflammatory hyperpigmentation pre-actively -- I mean, we can maybe prevent it by pre-treatment and treat it after, and perhaps as an exclusion criteria or a warning to patients that may be keloid-formers that they should not have this therapy.

So those are my conclusions.

DR. GERSON: Could I just ask the FDA if there's another aspect of this question that we need clarification on?

DR. WITTEN: No. Thank you.

DR. GERSON: Then let's move on to question number 3, other demographic characteristics.

The proportion of subjects over the age of 65

and male subjects in the clinical trials are small. Please discuss whether or not the data from the trials and your knowledge of the literature suggest any potential safety hazards with the use of this product in these groups.

Again, I'm going to ask Dr. King to help lead off the discussion.

DR. KING: Similar to the question about risk from the scarring in ethnic groups, it's now turning out to be that older people are getting to be the majority. The males that we usually allude to are males who are white or those who have less pigment, and so it's not uncommon to see cancers behind the ears, and in my dermatology practice, it's just unexpected there but you see it. And it gets down to good news and bad news.

The good news is that autologous fibroblasts carry minimal risk across all ages in my experience and permanent use of this usually leads to a good scar or repair. The bad news is tumor formation or acceleration is usually not induced in less than 12 months, so it may not be detected. Older donor skin

fibroblasts are actually slower to do things; that is, they don't move fast but they do move or we'd all be dead by age 65. So sometimes it takes a little bit longer to get up to the speed to produce tumors, so you're not really sure and the data's not there beyond 12 months.

The more bad news is the clinical efficacy in older patients may be less optimal because of dietary issues, menopause, UV damage, and so forth. So I think there's going to have to be centers of excellence. You're going to have to define your population. Otherwise, you're going to be out of business really quick.

DR. GERSON: Thank you. Maybe I'll just lead off. I have two concerns in the population over the age of 65. And that is, I'm not as comfortable with issues of efficacy in that population and I might be encouraged to suggest that assessment of efficacy is actually important in that age group because our knowledge of the biology, as Dr. King mentioned, as others have discussed, certainly would suggest that perhaps the response in vivo, despite the ability to

grow the cells ex vivo, may be more muted. And if it's an ineffective product, then it doesn't seem pertinent to pursue that. We don't have any other evidence of a safety issue, other than the ephemeral one of tumor genicity, and I don't think we have any reason to restrict or be concerned about male subjects.

DR. ALLEN: I have some reservations about the older population only because, although the cells, we may well be able to get them to grow, proliferate in vitro, the reality is that we don't really know that it's those cells that are actually making anything in there. They could well be just pumping out growth factors that are stimulating the local cells to do something.

So the reality is that it's the environment you put the cells into that's as important as the cells you put in. So if in fact the older population has a less receptive tissue mass, then maybe we're not going to see the effects.

So for me, it's not so much a safety concern at all; it's really about efficacy. And maybe it's as simple as just saying that, you know, the possibilities

of this working may be less in the over 65s until we have more data, but that would be my concern.

DR. DRAKE: I have a little different tack. I guess I am a little more concerned about this. I think efficacy is one part that shows it's not as effective in that group, but I think we have to ask ourselves why is it not as efficacious in that group. And that's a question that could have easily had some fairly -- some data that would be reasonably easy to capture had there been some biopsies post-treatment.

We don't know what's going on there, and I'm going to go back to that point. We simply don't know what's going on or what we're seeing. And the fact that the elderly are not responsive could be indicative that the elderly are also not as able to make scars as the younger people are.

So I think there's a bit of a lack of short-term data here to my satisfaction. I think other things could have been done in this study. Particularly, I think the lack of response in the elderly should have been a trigger, should have been a signal that somebody else needed to look at something

else to figure out why that was occurring, and that wasn't done. So I have some concerns about this.

The elderly also, their immune system and their whole response to almost any kind of injury is not as up to par as the younger people in many respects, and that may make them prone to something. And the other thing about it is we have not talked about other cells or other tumors, besides basal cells. I mean, if you're going to turn on something in this area, it's photo-damaged skin -- I mean, we've got squamous cells, we've got other things that can turn up in that area. And although this is primarily fibroblastic, we don't have any long-term data, or short-term data for that matter, to suggest we're not messing with other cells. So I have some concerns in this age group.

DR. GERSON: Dr. Chappell.

DR. CHAPPELL: I have no comment.

DR. NEWBURGER: I have nothing to add.

MS. RUE: I don't think that this age group should be excluded. I think this age group with levels of wellness vary greatly, with more people that age

having chronic illnesses than younger, more of them being on medications, different kind of medications than the younger population. But I just think it needs to be something that's taken into account and watched as opposed to have them excluded because of those factors.

DR. WOO: My concern about this particular age group is not so much from the safety side but from the efficacy side.

DR. GERSON: Dr. Drake, just one more.

DR. DRAKE: I hope my remarks didn't lead to anybody thinking that somebody should be excluded.

There's a fundamental rule. Once it's out there, everybody will use it. And so, if this committee -- particularly in wrinkles and particularly the older you get. So if anybody is thinking about approving this in any respect, then one has to consider that it will be used in every age group all the time and far more extensively than we would ever think. It's a very popular field, wrinkles, and having developed some, I can tell you.

(Laughter.)

DR. GERSON: Dr. Dubinett.

DR. DUBINETT: I agree with what's been said. I think, in addition to increasing a clinical population base in the age group, another possibility would be to begin to look at the characteristics of the cells in that age population under these culture conditions to see perhaps if there are clues about efficacy and perhaps safety.

DR. SNYDER: I pretty much agree with everything that's been said. I certainly wouldn't want to exclude the elderly and I think that should be a very relative term. It depends on their health.

I think it's intriguing that probably elder either tissue or cells may be less responsive. I think it's very intriguing and could be addressed by most of the things that have already been discussed.

I thought one thing that -- so I guess the way I would approach the older patients or the way we talked about with the non-Caucasian patients, either increasing the sample size either retrospectively or prospectively or both. And I thought that, Stanton, you actually brought up an interesting variable in the

patient population that we hadn't discussed, and that's smokers. In addition, they do increase -- my sense is that there's an increased risk of wrinkling in the smoking population. A lot of us, it's often attributed to poor profusion, I believe. So I'm just wondering whether that needs to be something that needs to be looked at, transplantation into smoking population, that may have poor profusion of that region and whether that might even account for some of the differences in efficacy could be a part of safety.

So certainly there's a higher risk of smoking in the non-Caucasian population. I think epidemiologically the non-Caucasian population often has higher smokers in it, too. So I think it's a very interesting point, in addition to the predisposition to cancer that you mentioned.

DR. RAO: I agree with Dr. Gerson's summary and I have nothing further to add.

DR. GERSON: Dr. Olding.

DR. OLDING: Nothing.

DR. KWAK: I have noting to add.

DR. BURKE: There was a study done at Duke

from Dr. Pennell's (ph) lab by C. Phillips that showed that elderly -- they studied neonatal fibroblasts after circumcision in vitro as opposed to elderly fibroblasts from biopsies of patients over 90. And they found that the elderly fibroblasts proliferated at about one-third to one-half of the rate of the neonatal, and they found that they produced one-sixth of the amount of collagen.

So this is possibly very relevant to the proliferation and the efficacy of the elderly cells. So that would probably be recognized as soon as the cells were taken and attempted to be cultured. and certainly the patients should be informed of this, and I think that each patient could be informed of the time it took for their cells to grow in culture and if there were some quantitative idea of how much collagen their cells produced when they were being reproduced in the 36 to 55 days or 60 days or whatever. So I think this is something that's important.

DR. TAYLOR: I think again the potential for transformation in these populations is significant and would recommend that the types of markers we discussed earlier and some of the genetic potential alterations

be looked at, especially given the low degree of efficacy.

In addition, with regard to men, I think it's important to look at the increased incidence of cancers as males age and whether or not some sort of testing for risk of something like maybe a PSA should be administered prior to use of cells, if there's something like that.

DR. ALLEN: As we go around, it becomes pretty clear that, in addition to death and taxes, wrinkling is inevitable.

It seems to me that one of the issues here is what are we going to recommend or what are we going to follow. And if the data's already there for age and population, then it seems the company would like to look back and see what is the correlation between the time of doubling and so forth. I mean some people at age 85, their collagen seems to me to be looking pretty good. I think the current phase is something like cougars. But I think that we need to look at data you already have versus what we need to do. And since people are not like mice, you've seen one, you've seen

one. And I think we have to be creative to find out because I think the ultimate issue here is are we introducing something into the cells, because the cells come whatever they are and the environment's going to whack them, whatever. And I don't think we're going to find, for example, keratinocytes still surviving if they're pan keratin negative. I think the company's already doing that.

So there are other cells that might persist or should be diluted out, but I think you can do a panel of some and find out what is a profile, like you do $500 per test immunoperoxidase stains and find it. I think that's really appropriate. And as somebody who's over 65, I would not necessarily want to be excluded.

DR. GERSON: Are there other comments?

Let me just re-raise or re-comment on the fact that this question related to safety concerns and we've heard a diversity of opinions, I think, about how to respond to the limited data on efficacy.

On the one hand, the sense that we wouldn't want to exclude a population; on the other hand, a lack of efficacy.

Is there any more discussion that we would like to have on that?

DR. ALLEN: I've just got one comment. And I may have missed it in the discussion, but one of the things that hasn't come out in what we've heard so far, at least to my way of thinking, is we've heard about the inclusion criteria for these study subjects having moderate to severe, but I haven't heard any discussion about -- we talked about on the grading it's hard to get from a five to a three than it is from a four to a two, et cetera.

But one of the variables that may be inherent in this is it may be -- and I'm not trying to be ageist here, because I'm still just under 65. But it may be that older patients have more severe wrinkles and it's hard to get that migration down from a score of X to a score of Y. So in fact maybe it's just a harder task. It's not that they may be less responsive but it's just a harder thing to do.

So it would be encouraging, I think, to see when you look at the data with a larger study population, to just look at the relationship between

the initial score and their responsiveness.

DR. GERSON: Thank you.

Dr. Olding.

DR. OLDING: I was going to save this discussion for the efficacy portion, but I was not surprised that their efficacy rates were not as good as the others because no matter what, when you evaluate, you're supposed to be evaluating one wrinkle or the patient's evaluating themselves. It's not just that one wrinkle you can focus on. You have a pallet of wrinkles and you only get rid of one, not the rest of the pallet. So it did not terribly surprise me.

DR. NEWBURGER: And to agree with what Dr. Olding is saying, this is a very difficult fold because it has a lot to do with loss of volume laterally and you're going to -- so even if you plump out the nasolabial fold, if someone continues to lose their malar fat, you're going to have that redundancy increasing. So it is a very high bar to reach. So that's worse in elder subjects.

DR. GERSON: I would also, I think, remember that the self-assessment improvement in one of the two

studies was different in the older population. It was the evaluator in both studies that was not. So perhaps, in fact, the self-assessment was commenting on the recognition of some benefit.

So are there other comments? Yes?

DR. TAYLOR: Maybe we heard these data earlier and I missed it. Was there any association with age or sex and the failure of the biopsies to grow?

DR. GERSON: That's what I was asking.

DR. NOVAK: No.

DR. GERSON: Have we addressed the question to the satisfaction?

DR. TAYLOR: Yes, thank you.

DR. GERSON: Thank you.

We're going to move on to question number 4, which relates to physician training. Thank you.

The available safety data demonstrated a high incidence, up to two-thirds of the subjects, with injection site reactions. Those events tended to last longer in the IT-treated patients than in the vehicle control group. About 6 percent of events in the IT group lasted beyond 30 days. Such events may cause

cosmetic concerns. The applicant notes that proper injection technique may play a role in the frequency and severity of these reactions. The applicant is proposing a physician training program as a requirement for the use of the product. And we have two items to discuss.

Do you have specific recommendations for the content of a practitioner training program; and, second, do you have any other recommendations in how to minimize these adverse events and presumably that would be through a training process.

We've asked Dr. Newburger to lead our discussion.

DR. NEWBURGER: First off, I'd just like to say that what's called a high incidence, up to two-thirds of subjects having injection site reactions, is not a high number when one is looking at injectable fillers because it is not unusual to get bleeding and to get swelling, to get sensitivity, and all of these are reportable.

The issue with injection site reactions should be separated into short-term and long-term reactions,

and we don’t yet have that profile. Of course, longer-term reactions are going to present a cosmetic concern. People are very forgiving if they think that something is going to go away, even in the first month.

But in terms of contents for a practitioner training program, I think that there has to be in the training program very specific injection techniques. I think that these techniques should be studied to show what is going to give the maximum response because there is a dichotomy of responses in the earlier studies prior to this product; that is to say, former Isolagen and this product.

I think that there has to be care in the handling of the product, not only in terms of how the biopsies are done and preservation of sterility but also perhaps something as simple as how do you prevent settling of the suspension as it’s there in the syringe while you’re waiting for the patient to have the topical anesthetic effect. I think a video, in addition to the onsite training, could be a very good thing for people to refer back to.

Recommendations for reducing post-inflammatory

hyperpigmentation, I've already made some suggestions. It's easy to just ask if someone has a history of herpetic lesions, and if they do, to put them on prophylactic antiviral. But what's been mentioned here is that once the product is out, it's out. We've seen that happen with quite a few other products for improvement of aesthetics of the face. And I think that there is a built-in quality -- rather, I think there is a built-in control, that it wouldn't be necessarily used in too many other locations because there is a limitation in how many cells are going to multiply.

So it isn't like you have an unlimited supply that all you have to do is call Allergan or Medisys or Dermac and you can order your injectable wrinkle filler. This is going to be a limited supply for each individual based on the quantity of cells that is produced. And perhaps it would be appropriate for the company also to get a verbal or written confirmation from the practitioner that, indeed, the product is only being used in the indicated site, because I can foresee all kinds of aesthetic -- other problems if it's used

in an area that's traditionally thin-skinned.

DR. GERSON: Thank you. So you might include that in the training activity?

DR. NEWBURGER: Yes.

DR. GERSON: And could I just query? I noticed that the training program verbiage is all around the practitioner. As a dermatologist, is it important to include the healthcare assistance in an office setting or is this really all done by the practitioner themselves?

DR. NEWBURGER: That's a very hot political question right now. There's a divergence of who does aesthetic injections in facilities all across the country. I'd like to say that only physicians do it, but in practice that's not the case.

DR. GERSON: And what about the preparation of the material prior to the actual injection?

DR. NEWBURGER: Other products do not require much preparation with really one exception currently, and generally that preparation is done by a nurse or an assistant.

DR. GERSON: So if I could go around.

Ms. Rue.

MS. RUE: The only thing on that line is if there's going to be assistance in the office assisting the physician, that they need, I would think, to have some documented training, whether it be provided by the physician or not, just to show that they were instructed appropriately.

DR. WOO: I guess nobody can be against training. So I have no issue about the injection site reactions, even those up to two-thirds of the subjects, as long as it occurs with the same frequency between the product and the vehicle control.

My concern has to do with this long-lasting effect when you have 6 percent of the product-treated group that develop this reaction, which is absent in the vehicle control. And, therefore, to me, the cause of this longer-term reaction is the product itself. It has nothing to do with the injection technique, assuming that it is the same individual who is doing the injections of the product and the vehicle.

So I'm not so sure the long-term effects of the 6 percent can be taken care of by training.

DR. GERSON: Might you help us with the suggestion that practitioners be trained in long-term assessment and, if necessary, reporting?

DR. WOO: Reporting for sure, but I'm not a dermatologist, so I don't know how to recommend in terms of what can be done to reduce this frequency of long-term effect.

DR. DUBINETT: So I agree with what's been said and I guess I have a question for the sponsors.

The statement that the applicant notes the proper injection technique can play a role in the frequency and severity of these reactions, is there something that you know that we haven't heard about yet where you have specific knowledge of a technique problem?

DR. BOSS: Thank you. The injection technique, as I briefly mentioned before, is important in a couple of ways. One I heard mentioned was topical anesthetics. I've found that with topical anesthetics, that can be a basal dilator and increase the amount of bruising and bleeding at the injection site, which we like to avoid. I usually have used ice prior to the

injections.

I think also the proper delivery of the material, if it's delivered too deeply, it's going to go into the subcutaneous tissues where it's not going to be active or appropriate for the therapy that we've designed. So I think the injection technique is important to maximize the efficacy and minimize the potential complications.

DR. DUBINETT: So it sounds as if, even beyond similar procedures for other types of indications, that more training would be necessary for this than the usual.

DR. BOSS: I'm not sure that I understood your question.

DR. DUBINETT: In other words, is there specialized training for other filler agents?

DR. BOSS: Oh, yes. Different fillers, as has been mentioned once before, are recommended to be injected in different levels. As was mentioned, some are recommended to be at the dermal subcu junctions, some of the deep dermis, some of the more superficial dermis.

So depending on the filler that's being used and that's in the bulk filler categories, it's specific recommendations for the attempted site of therapeutic injection.

DR. DUBINETT: So I would concur then with what's been said regarding the training.

DR. SNYDER: Yeah. I don't think anybody can be against more training. I certainly have done plenty myself.

I would recommend, in addition to -- and echoing some of the things that have already been said, that in addition to training and administration, that the practitioners should be trained in screening for adverse reactions. They should know how to pick those others apart as opposed to the pretty much anticipated local reactions that one would see.

I think training should also include proper selection of patients and screening out patients that are inappropriate, how to prepare the product. And I would think that everybody involved in the procedure, physicians and non-physicians, should be included in the training. I think if one can make it mandatory, I

think that would be important.

DR. RAO: The only thing I thought to add to what was pointed out while preparing the product is that with cells, one big difference between fillers and everything else is that cells aggregate and then they get clumped together and you change your viability. And I think it has to be really emphasized in training and when you prepare your product and how long before you do the injections, because in a busy office that's always an issue which you often don't have control over.

DR. OLDING: Since we don't know really again the mechanism of action, it's hard to say that a particular training technique will make a difference in the complications, especially when, in fact, if you look at some of the other injectables, as Dr. Newburger has said, those initial reactions are even more commonplace, I think, than with this particular product.

But sort of like I tell patients who have capsular contracture, and why did they get it and why can't we cure it, well, we don't know what causes it.

So until we know what causes it, we don't know what to cure it with. So I don't think I have any recommendations on how to minimize the adverse effects.

DR. KWAK: So the statement's been made that once the product's out, it's out, but I think that doesn't really apply here, because you have an autologous product, the sponsor has an opportunity to really regulate who gets that product. And so, I think it goes, yes, for sure training, but I think it goes beyond training, and Dr. Newburger has made some of those points already. So you have an opportunity here to regulate off-label use, to really monitor adverse reactions. And so, I think, yes, training, but it goes beyond that.

DR. BURKE: There's no doubt that training is absolutely essential, first in not only the biopsies and treating the cells, maybe even with more sterility than the usual practitioner might know. But also, we know with all fillers, the efficacy is technique-related immensely and the adverse reactions are very much technique-dependent. And with the cells, you have the additional cells themselves from each individual

patient.

So there's no doubt you need really excellent training, and that should be mandatory. And perhaps it should be that only physicians take the biopsy and only physicians inject it because now we're talking about a level more than a pre-made filler.

DR. TAYLOR: We all know that training in a clinical setting is more likely to be successful if it's done by someone who's done a large number of procedures, similar procedures. So I would recommend a threshold number of procedures that an individual has to have done and a center has to have done before they can be a training facility. And if there's a high incidence of adverse events at a given center, that that center be disqualified from being a training center for a period of time until that is rectified.

I would also recommend that the screening for and looking for adverse events be part of the training procedure. And then, finally, with regard to recommendations on how to minimize these adverse events, we've talked about needle size, we've talked about location of injection. I think it's critical to

think about pressure flow, all of the things that we know affect how cells behave when they go through a needle and go through a syringe, and I think we ought to be giving timeline guidance with regard to the rate of injection as well as the location and depth of injection.

Then, finally, with regard to recommendations on how to minimize adverse events, we've already heard that the vehicle's been altered to some degree, to wit, removal of penicillin. I would argue that going forward, the vehicle is probably one of the critical components with regard to site injection, given the number of adverse events in both groups.

DR. GERSON: Thank you.

Dr. King.

DR. KING: I guess I have to disagree with the thought that not much is going to happen and that the sponsors can regulate off-label use. I mentioned several billion dollar settlements by the government against manufacturers about promoting medicines off-label.

I disagree also when it says physicians

training. It's been my experience traveling around the country looking at programs, I would say most of these kind of things are dependent on injection expertise. It's not intellectual expertise. So a lot of what I'm hearing here is when we inject things, we get holes in the skin and they leak and some people have bad reactions and some don't.

So I would like to have some information about what's going to be those group of patients that are going to be excluded. Every time you do a drug study, you get indications and you get exclusions. And I haven't heard a lot here, and I certainly didn't want to have the over 65 excluded, but it seems to me there has to be some more form of buy our product and inject it and you'll look wonderful, you know. That's not quite the way I think about it. And if you're going to say physicians, that's physicians, and that to be an FDA-type thing because some procedures can only be board-certified. But I suspect on cosmetic kinds of things, it's going to be a whole lot of trained assistants. And so I don't want to get into that issue because it's a huge issue of who's qualified and who's

trained. But there has to be some thought about who's going to inject this and whether the company's going to have the right like franchises to disenfranchise groups. That's a big issue.

DR. GERSON: Thank you.

Dr. Allen.

DR. ALLEN: I think I'd just echo the thoughts that are being said. I think that in reality it's going to be hard to limit this to physicians. I think it's basically whoever is administering the injections. They should all be done under the care of a physician. So whoever's doing it needs to be appropriately trained.

I think it's important that they're trained in recognizing the signs of adverse events. I think it's also important to think about the concept that maybe -- and I haven't seen any of this in the data, but maybe there are some preemptive signs, perhaps on the first injection, if there's an unusual adverse event, maybe that's the patient that needs to be watched and maybe even that patient doesn't get a second dose.

So I think as we get more data on whether or

not there is a relationship between these signs, we might get some more information about who's a good candidate for completing and who's not. But I think it's critical because the success of this is not going to be based on the efficacy. If it is in fact relatively low efficacy but it matters to some patients. And certainly a high incidence of adverse events that could be controlled will kill the market share.

DR. GERSON: Dr. Drake.

DR. DRAKE: Well, I want to compliment the sponsor for taking on this task of trying to educate physicians. That's sometimes a huge challenge since I live in that world. I just want to thank them for doing it. I think it's a tremendous challenge, but I agree totally with Lloyd.

I don't think we can put a sponsor of any product in the business of regulating who uses it once it's out there, any more than you regulate whether it's a physician or a nurse practitioner or a technician, for that matter, or whether it's a dermatologist or a plastic surgeon or an internist. I mean, I just think

it’s very tough. You can’t get in the position of putting a sponsor -- I don’t think you put them in the position of trying to regulate that.

DR. CHAPPELL: One way to address the issue of whether further training is needed is to see whether there are site differences in adverse events in the clinical trials. But we weren’t given site-specific rates and I don’t blame them at all because the events that we’re interested in would be rare enough that that would be relevant.

That’s why I focus on efficacy, which is, of course, of interest in its own, and I’ve already said that I made a plot of efficacy for the 13 sites Dr. Lee provided us with data on efficacy, both the medical evaluators and self-evaluation. And the medical evaluators’ ratings were correlated for the IT and the placebo group, so there were good sites or bad sites. But it could just mean that their evaluators tended to rate high and some evaluators rated low. And so, that’s my question to Dr. Lee about equivalent data for the subject self-ratings, which she provided me and so I did the same kind of plot over lunch which I also

have. It's verified, I also have on my computer, and it seems that patient evaluations for the treated group are completely uncorrelated with patient evaluations for the control group, which means for patient evaluations, you don't have good sites and bad sites. They have about the same effect of -- the treatment has about the same effect, regardless of the control, which seems to me to indicate, just on an initial basis, that it's the raters that varied.

So if you're going to train anybody based on these data for your next clinical trial, you have to train the raters very carefully. So I'm back to agreeing with your explanation that it's very hard to get the raters standardized.

Why do I focus on efficacy rather than safety? It's because efficacy, first of all, evidence of efficacy is much more common and, secondly, my complete guess, that efficacy depends on you injecting and you administering the treatment well, and safety depends on you administering the treatment badly, plus also bad luck perhaps. So if you don't get it where it's supposed to be, it will be subcutaneous somewhere where

it isn't.

So I don't have concerns now, and I urge the FDA and the sponsors to continue to examine variations in efficacy as being important for its own sake and related to safety.

DR. GERSON: Dr. Newburger, could you help us summarize this discussion?

DR. NEWBURGER: Everybody agrees that additional training is de rigueur in learning how to do this very sophisticated technique without having undue adverse events and having optimal outcome.

Everybody has, to a greater or lesser degree, some concerns about who will be doing the procedure and whether they will be appropriately trained, i.e., maintenance of sterility, tissue specimen handling, and then when the product comes back to the clinic, that that product will be handled appropriately. And most people have concerns that the product will be used off label.

I have a question for Dr. Witten.

Can CBER restrict the use of the material to site or amount? CDRH cannot restrict once a device is

out, but CDER can and does with certain drugs, limit who receives the drug.

Does CBER have that ability?

DR. WITTEN: We have certain post-market abilities. And, actually, I'd like to ask Craig Zinderman, who is one of our post-market experts, to, rather than just answer your question, maybe give a little explanation of what our post-market authorities are.

DR. ZINDERMAN: In general, as you commented about CDRH, FDA does not have the authority to restrict off-label use. Once the product is licensed, it's licensed to be used for the approved indication and the only extent to which we can restrict that authority is restricting the sponsor from marketing the product to be used in off-label uses.

There are authorities that FDA has to restrict the distribution of a product and that might what you're referring to with respect to CDER. If there is a specific serious risk that's identified, then there are strategies, such as the REMS, the Risk Evaluation Mitigation Strategy, and those can have some elements

to assure safe use so that the benefits outweigh the risks. There are certain criteria that have to be maintained. Those REMS are designed to mitigate, as I said, a specific serious risk.

DR. WITTEN: Do you have more questions or do you want some examples or something?

DR. NEWBURGER: Well, if the risk isn't yet identified or characterized, would this particular product be able to be regulated in that way?

DR. WITTEN: Well, that's a slightly different question. I think what Craig was just describing were if we are at the point of approving a marketing authorization or license for a product, what additional things can we put into place?

One of them is REMS, and we also have certain post-market studies that we can require, but we first have to get to the point of deciding that the product is suitable for marketing in terms of its safety and effectiveness, which are the next two voting questions.

But in terms of if we have decided to grant a license, then these are things we can put in place, what he described as well as some - you know, we have

some options for requiring some post-market studies, which, if you are interested, Craig could give us a short description of those, also.

DR. NEWBURGER: Thank you.

DR. GERSON: Could I just further interrogate that response?

So if, in the hypothetical, there was an indication, such as the indication that's before us today, and it required a biopsy, the logic to me would be a request that the sponsor be informed by the practitioner that the biopsy was for the indicated use. And that isn't, I'll use the words "advisedly foolproof," but it would provide some level of information about the intended use.

DR. WITTEN: Well, I think what Craig said is correct, which is they're not -- you know, physicians can use these off-label. The sponsor can promote it for off-label use. If we saw post-market a certain amount of off-label use occurring, we might ask for additional studies or encourage the sponsor to develop data for that indication.

DR. GERSON: Dr. Kwak.

DR. KWAK: I think that's the important point, is that there's really no precedent to my knowledge, correct me if I'm wrong, for an autologous product where the biopsy's required to provide the starting material for the drug in this case, so might you not have a unique opportunity here to break new ground in terms of post-marketing regulation.

DR. WITTEN: Well, can I mention we do have a product that meets that, which is Carticel, which is already on the market. In terms of regulation, regulations aren't for specific products. So if there's something that you think we need to do to ensure safety for this product, what we would request that the advisory committee do is describe the risk or the concern -- if it's, as you say, not a defined risk; describe the risk or the concern, give us advice about how we might best meet that concern or address that risk, and then we can take it back and look at our existing regulations, which I think can cover most situations and we can figure out how we might address those in this case.

So what we'd like to hear are the safety

issues or the concerns about unaddressed safety issues, if that's the case, and what you recommend would be the best way to address these.

DR. GERSON: So if I could, what I'd ask is that we defer this discussion as the third component of the next question, which is about safety and part of that question requires a vote.

So if I could, I'd like to come back to this at that point.

Dr. Taylor.

DR. TAYLOR: Could I just ask? I think I heard a word I didn't understand. I think you said you can't promote off-label use. Does that mean advertise or what does that mean?

DR. WITTEN: Yes. The sponsor can't advertise or encourage off-label use.

DR. TAYLOR: And would growing a biopsy be considered promoting?

DR. WITTEN: I'm not a compliance expert and you're right that this is a different situation, but let me just tell you, in general, what that means. And, in general, what that means would be if a sponsor

has ads out, they go to physicians' offices and they put it on their labeling material and they list some other indications for which it isn't approved, that kind of thing, that would be promoting.

If a physician requests a product -- this is like any other prescription. When the physician writes a prescription, you can think of it as writing a prescription for a product to get the drug company to supply that drug, they're not required to put down the diagnosis which they're planning to use it for for treatment. And so it's just they want the drug, they write a prescription for it, and they get it.

So what we would aim at doing, and most of these post-marketing risk management-type plans are aimed at doing, is promoting safe use, but that's not the same as asking the pharmaceutical company to police off-label use. So that's generally been the approach and I think that would probably be the case here, too.

DR. GERSON: Dr. King.

DR. KING: It's been my experience, particularly in terms of off-label use, that when you develop some new device, such as lasers, they have

week-end 24-hour go-to Orlando or Hawaii or some neat place, and you come back certified to use that product. And you may not say that's not promotion, but it certainly comes under the category of inducement. So if we're going to have centers of excellence and so forth, it seems to me that it has to be more than come learn how to do some injections in 24 hours, which you basically have to do to graduate from medical school or nursing school.

So you're saying that there's no regulation for that kind of a promotion?

DR. WITTEN: Well, what I'd say is that if there's some specific things that we think should be included in a training, or you as an advisory committee member thinks should be included in a training program, we'd like to know what they are and make sure they're implemented. In terms of where it is or how it's conducted or that kind of thing, I think we're not really going to contribute much to that, to where they have the training. But if there's some specific elements for training, like I heard about doing observed injections, or some specific elements you want

to mention that you think should be part of the training, then that's what would be helpful to us to hear about. But I do understand the concern; however, that's just really not part of what we have oversight over.

DR. GERSON: Have we otherwise addressed this question? If you would allow, I'd like to move on to question number 5.

So question number 5 is the first of our two questions in which we will in fact use our newly-acquired voting skills, and let me read you that question and remind you that it's three parts. What I'd like to do is have the discussion, I think, of all three parts and then have a vote. And if we need to go back to the second and third parts, then we will do so.

So question number 5, 21 CFR 601.25(d)(1) states that "safety of a licensed biologic product means the relative freedom from harmful effect to persons affected directly or indirectly by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time. Proof of

safety shall consist of adequate tests by methods reasonably applicable to show the biologic product is safe under the prescribed conditions for use, including results of significant human experience during use."

So the discussion and then vote will be on the topic, do the data presented demonstrate safety for the proposed indication, and then discussion. If no, what additional studies should be performed? If yes, do you have specific recommendations for the labeling?

I'd like to lead off this, now that we can see this question, with a discussion by Dr. Drake.

DR. DRAKE: I think this is at the heart of this issue for me. I think the big issue here is that there are lots of unanswered questions, lots of unanswered issues.

I think there's a song about unanswered prayers or something like that, but I felt like this was a lot of unanswered things. And so as I was thinking about why was I having this level of discomfort with this, and I think I can sum it up by saying what we saw today, which I compliment the company on showing us this part, was they showed us

lots of visible stuff, everything that we could just see. You could see the injection reactions.

Now, I agree with Dr. Burke and others that the site of injection reactions don't bother me because when you're injecting stuff, these things happen and I don't think they're out of the norm. I think what's bothering me more is what were the non-visible? We saw lots of the visible changes but we didn't see anything about the non-visible changes.

If you're looking at kidney disease or treatment for kidneys, you don't just look at the urine. You don't just look at something. You want to know what their creatinine is and you want to know what their urine shows. And we didn't see anything of the non-visible support for safety, and I think that's what concerns me most.

As we've mentioned, when something for wrinkles gets out there, it will have widespread use and it will be used for everything in the world, and we'll have no really control over the location. They'll use it in some locations where it may not be safe.

I think we have lots of unanswered questions here, and I want to draw your attention to the part of the question that was read, but I'm going to repeat it. It says, "Proof of safety shall consist of adequate tests by methods reasonably applicable to show the biologic product is safe under the prescribed conditions of use, including results of significant human experience during use."

I don't think we've met that standard here today. The standard, at least among dermatologists, is we would like to see -- we want to know -- all we've seen today is what happens at the initial time and then a clinical impression and/or photo at the end of it. We know nothing about what's happening underneath. Like I said earlier, I don't know what I'm looking at and I think we should know what we're looking at.

So, as I mentioned, are we looking at scar or normal tissue? Are we looking at collagen, what type? Is there any elastin, any effect on the elastin? What are the markers? We don't know any of that.

There are lots of other questions here, such as cell survival, migration, phenotype, proliferation,

regulation, transformation. I don't think we've had any of those questions answered. We haven't questions answered to my satisfaction about processing, and I'm not even a fibroblast culture person and I feel uncomfortable not knowing the answers. And I can't imagine that people who are experts don't have more questions about that sort of thing.

We don't know anything about the viruses or serum growth factors or anything. We don't have any information is this a remodeling process or repair process, scar formation. I just don't know.

So the standard of care in dermatology is to look at something before and after you treat it and see what's going on, and we don't have that information. And I think that such a standard of care -- I think it was a protocol design. I don't want to saw flaw, but to my mind it certainly should have been an incorporated part of any protocol to look at something as new and, frankly, as creative as this.

I mean, I want to compliment the company on coming forward with something as interesting and creative and thinking outside the box and good for them

because I'm going to get wrinkles, as I said earlier, and I want to have stuff for it. But I'm a little uncomfortable at the level of what we've seen today because all I've seen is visible. I've seen nothing deeper than that.

So, in summary, I think we're a little short on short-term data. I think we're way short on long-term data, and I think there's some deficiencies in information about processing that I have a level of discomfort with.

DR. CHAPPELL: I have nothing to add to Dr. Drake's comments.

DR. NEWBURGER: I agree.

MS. RUE: I agree with Dr. Drake.

DR. WOO: In addition to those, I'd like to know -- because these critical Pivotal Phase III trials, there are certain inclusion criteria and there's certain exclusion criteria. And so if the product is approved, I'm wondering whether these criteria will be applied in the application out in the clinic.

Do we exclude the potential patients with a

history of active autoimmune disease or organ transplantation and a whole list of things? So these are my additional concerns.

DR. DUBINETT: I agree, and particularly to the point of long-term follow-up data.

DR. SNYDER: I agree with what Dr. Drake said about wanting to know about obviously the fate of the cells and the fate of the host to which they've been transplanted. I also think that a little bit better characterization of the cells prior to transplantation is quite easy to do, just looking at number of divisions, karotype, the amount of collagen or elastin they produce, some of the markers that Stan mentioned in terms of whether or not certain tumor suppressor genes are kept on. It's very easy to do and it certainly would give us all a level of comfort.

DR. RAO: I have nothing further to add to Dr. Drake's summary.

DR. OLDING: I agree.

DR. KWAK: I agree that there's some unanswered questions about product characterization and whether adventissual agents are introduced in the

production process, but I think fundamentally this is an autologous product and I haven’t seen anything in the data that would make me think that it’s not safe. So I think it’s safe.

DR. BURKE: I agree with everything that Dr. Drake said so articulately. And I just want to point out that since each patient is sending his or her own cells, that patient could get information about their own cells as to certain cell markers, as to the time of proliferation, just as we do bone scans and we know relative to the norm how much osteoporosis you may or may not or osteopenia. They could know the timing of division, the timing of synthesis.

Again, I compliment the company. It seems that this is a very good therapy with relatively few side effects that we can see on the surface and short-term side effects. So all of that is extraordinary and we all want this kind of product now. The fact that there’s not major -- I don’t think anything -- we don’t want anything with infinite long-term efficacy because that means possibly side effects.

The non-biologic things that do not degrade at

all are the ones that cause the side effects 10 to 20 years later. So the fact we don't expect the wrinkles to be treated perfectly and for that treatment to last for many, many years. But the efficacy in some of the patients seems excellent, but it is relatively easy to do some studies in humans, as Lynn Drake so articulately stated.

DR. TAYLOR: I'm a strong proponent of autologous cell therapy. I have been for many years. I think it's safer than the alternative at present. I think I agree with what I heard Dr. Kwak say, that it probably is safe. I also think that I agree with what I heard Dr. Drake say in that there really -- it seems to me that with the storage of samples, it'd be very easy to answer this question. If the samples have been stored from the majority of these cell populations, it sure seems to me that a thawed sample could be karyotyped. These cells have all been grown. They could be karyotyped. Some of the tumor markers could be evaluated by PCR or by kits and standard assays. And if the answers were available, the question would be put to rest and I think we would understand safety

at a much greater level than we do now.

These are not inordinately expensive or inordinately time-consuming assays and I certainly think that they don't really increase the burden to the sponsor but really increase the comfort level of me anyway.

DR. KING: I come down on the side of it's autologous and it probably is safe. I'm also reminiscent of practitioners giving arsenic in the early '30s and '40s and developing lung cancers 20 years later. So I agree it's good to see the roof, but you worry about what's in the basement. So I also come down on the side of Dr. Drake saying you already have the samples. You already have the means to do an experiment. You don't have to go back through the very expensive R&D process of getting more injections. You just want to analyze what you already have.

DR. TAYLOR: I also just forgot to say, if this therapy is approved, it will be the second autologous cell therapy approved. It will be highly visible. It will have a significant impact on the field should it not be safe, and I think it's

imperative that we think this through carefully as we're evaluating something that impacts not just these patients but potentially a field. So I just want to add that.

DR. GERSON: I wonder if I could reflect some of the comments.

As part of the question, we were asked for additional studies. That was stated in the context of, if no. And I think what we've heard is uniform desire, if yes or if no, for additional studies about the product so that there's some angst over what the product is exactly in order to have a sense of safety.

So then if I go back up in my own thinking about do the data demonstrate safety for the proposed indication, the answer is yes and I think so. So the product is largely safe. The side effects that we've seen, even those that have lasted more than 30 days, don't seem to be terribly material, except in an idiosyncratic state, so we can't really see a trend developing or forming. It sort of passes the sniff test as a product.

The challenge is the proposed indication,

which is certainly not a disease or a life-threatening process, et cetera, and therefore our bar for safety should be quite high or low; i.e., we should expect it to be really quite safe for as long as we can imagine since we're dealing with a wrinkle. And as we've heard, there's a reasonable likelihood for other uses, and, therefore, if there's a safety concern that we don't know about, we'd like to bend over backwards on limiting that risk.

I would also agree with Dr. Taylor that if we are helping establish expectations and precedent for the use of autologous cells, there's a global sense around the table, I think that I've heard, that we'd like to know more about those autologous cells as they're being used.

DR. ALLEN: I'll just weigh in. I guess I've been struck by the pretty much complete absence at least of presented data involving animals, without sounding too much like a stuck record. If we don't have animal data, I'm fine with that, but we need some sort of data on the tissue. And to me this is true both for safety and efficacy.

I'm uncomfortable at this point that we have any understanding of what's going on, and as the chair said, I think the bar for this particular product, which is for aesthetic and cosmetic use, is pretty high. We have to be pretty sure.

So I see situations. There are products, like Carticel. I remember being part of the Carticel discussions. And the level of concern over safety and efficacy with that autologous product when used in cartilage was significant, and that cartilage is well buried inside your body, not visible. And we talk about these skin conditions being easily visible. It may be easily visible, but if you ended up with an oncologic thing going on on your face that's malignant, the deconstruction removal of that and reconstruction of your face is not trivial. For example, with Carticel, we can look for non-invasive tools and say what's going on at the tissue level.

We don't seem to have any way of doing that with skin. And so, I think it absolutely mandates that at least some subset of patients at some point are going to need to have some biopsy data. And I know

that's going to be a hard sell, but I think there's an absolute need for it because I just don't see -- all we're getting is what we see and we need to know what's going on underneath. And I think the sponsor needs that information, as well. They need to understand the biology of this and biopsy is the way to do it, as egregious as it may seem.

DR. GERSON: We've gone around and I'd like to now open for other comments and discussion. We have three portions of a question to query, and as I had mentioned, I'd just as soon that we got most of the perspective out before we voted.

Go ahead.

DR. DRAKE: One of the responders commented on my comment, and I want to make sure I'm clear on that.

I don't think the company has all the data they need for us to look at it. I think they have a lot of stuff they could look at without an undue burden. But what I'm talking about is you need a biopsy pre- and you need a biopsy post-treatment after a few months so that you know what's happened in the skin. So they may not have that, but again that's not

an onerous study to do. I mean that could be knocked out pretty quickly.

DR. NEWBURGER: And a biopsy does not have to come from an aesthetically-treated face. It's perfectly acceptable to do it from a forearm, from another site that's not cosmetically important, and you do serial biopsies.

DR. SNYDER: That's exactly the comment I was going to make, was that one can imagine not wanting to do a biopsy for a cosmetic procedure for the face. That's why you had the procedure to begin with. But one could do the biopsy from almost any area and have it be informative.

DR. GERSON: I'm confused, if I could, about where the committee's sort of comfort zone is and whether we're on the order of building a consensus about required additional studies during the research and development phase or whether there's a sense of, as we heard some folks say, safety of the current product and insecurity about just how safe it is, given the lack of fundamental biological information.

So maybe I could ask for a little bit more

discussion on this comment or this discussion question. If no, what additional studies should be performed? That's the question we were asked. In my own mind, it could also be, if yes, what additional studies could be performed. But I just need a little bit more discussion, if I could, on that.

DR. BURKE: I just think it's imperative to see the fate of these cells in vivo in humans. And they're already taking retroauricular biopsies to generate the fibroblasts in vitro, and so I think that it's relatively simple to then place them retroauricularly and do sequential biopsies to see what is happening, to see what the cells are doing. Are they proliferating and are they producing -- first, are they viable?

Second, if viable, do they themselves proliferate? And three, what do they produce? Do they produce Collagen Type 1 or Collagen Type 3 or elastic tissue or hyaluronic acid, et cetera? So we have markers for all of these things. So I think that is absolutely important, and I think also if there were some way to go back on these sub-populations. There

are populations of people in the United States that had this implanted 14 years ago. There are populations in the U.K. five years ago. So I think can we look at some sub-populations and see what is happening.

Third, I think if and when this is approved, I think that somehow the individual should know how good their cells are with respect to the norm in proliferation, in synthesis of collagen, and they should know what markers there are, especially males. And males get sun damage behind their ear, so they're going to have P53 and P16 damage, and it's of interest to know what percent. Because we know above a certain percent, it's pretty certain they'll get actinic keratosis and maybe even a squamous cell, and there are markers for basal cells. So there could be something stated about at least the individual gets a report about certain parameters so they know what to expect.

DR. NEWBURGER: I agree with what Dr. Burke has said, and I think because six months is really a very short period of time, even when you're looking at wound-healing, if the action is from a wound here, I really would like to know if this is a gift that keeps

on giving.

Do these fibroblasts keep pumping out whatever extracellular product they're making? I'd like to know what the long-term potential is, because how do I know that someone won't develop ridges eight years, 10 years down the line? I'd like to know. I think that's important.

DR. TAYLOR: On the question of safety, I have not heard any data and this came up from Dr. Woo, and I believe someone else on that side of the table and I forget who, I apologize, with regard to smokers. We've not heard anything with regard to people who are known to be at increased risk of scarring. And so I guess the only populations in which I feel like I can speak to safety are primarily white females in a given age range that comprise 90 percent of the patient population. And in that context, I think at least with regard to short-term side effects, I haven't seen anything that convinces me it's unsafe.

That being said, I think the studies that we've heard -- I'd defer to my dermatologist colleagues for what the standard of care is in this field.

DR. GERSON: Dr. Woo, go ahead.

DR. WOO: I would just like to amplify the chair's comment, that this is a novel product for a disease indication that is not life-threatening. So therefore, to my mind, the safety bar should be very high.

DR. SNYDER: I think almost everybody feels that this is relatively safe. It has enough efficacy to be warranted and is an important advance for the cell transplantation field and will get a lot of attention. And I think there are just a few gaps that are pretty easy to fill. It's certainly the minimum level for any kind of transplantation study many of us have dealt with. This is just the minimum amount of knowledge that any transplanter would want to know, which is what is the fate of the cells.

So to answer your question, I think we all feel basically like we're moving in a direction of probably saying this is okay. We just feel a lot of discomfort in having these easily-filled gaps in our knowledge.

DR. GERSON: Thank you. Let me move your

direction just slightly -- I'll come right back; let me get this thought out or else I'll forget it -- to the related topic in this section of specific recommendations for labeling, if there's any other comments people want to make before we move towards a vote.

Ms. Rue.

MS. RUE: This is not about labeling, but I just wanted to say we're talking about wrinkles now, but the sponsor alluded to using this for burn scar therapy, I think, and that can be life-changing for people. And we're also talking about something that may be utilized in a significant population, and we really need to get this right because that has huge potentials for those populations.

DR. GERSON: Thank you. If there are not other issues that are burning, then what we might do is to go ahead and call for a vote.

Is there another comment before I do so? One more comment. Yes.

DR. RAO: I just wanted to suggest that we rephrase that first question. Do the data presented

demonstrate safety? It should perhaps be do the data presented provide adequate demonstration of safety, right, in some fashion because it's not that the data don't provide evidence of safety, they do, right? And if I look at that data and the side effects, it all looks fine, but the question is is that all the safety data you want to see, right, as opposed to anything else.

Unless the FDA has objections to the wording, because otherwise when we went around the table everybody was sort of, well, it's okay, but we have additional questions on both sides of the table when we talked about what Dr. Kwak pointed out and what Dr. Drake pointed out.

DR. GERSON: Let me suggest, if I could, that your vote reflect your modifier. My hunch is that, as we add on the fly modifiers to a question, we get ourselves into trouble. And so I'd just as soon not change the wordage, but you can reflect that in how you vote.

DR. BURKE: I just wondered if we could vote separately on 5-A, B, and C because I think we all have

different answers to does it seem to be safe, but does it need additional studies, and can we recommend the studies. And I think that's all come out of this conversation, but to just vote on all of 5 as one thing is very --

DR. GERSON: So the vote is on, as it states, demonstrate safety for the proposed indication and the comment and discussion is on the other two elements. So we don't need a consensus. We need discussion of the other two topics is my interpretation.

DR. TAYLOR: Point of clarification. Can you just restate what the proposed indication is and are there exclusion criteria for that -- patients who are excluded from that?

DR. GERSON: Rather than me making that up, maybe I can ask the FDA for that clarification.

DR. WITTEN: The proposed indication is treatment of moderate to severe nasolabial fold wrinkles.

DR. TAYLOR: And that's in any population?

DR. WITTEN: In adults. Sorry. In adults.

DR. GERSON: Dr. Woo, did you have a comment?

DR. WOO: My comment was that I'm opposed to the concept of changing the questions before we vote. I don't think the questions should be changed. We should just vote according to what's being asked. Otherwise, you get into trouble every time.

DR. CHAPPELL: I agree and it's happened.

(Laughter.)

DR. SNYDER: I'm a little bit confused about how to vote. I mean, in a way I regard this as like an NIH grant that needs to come back for its A1 revision. You're probably going to fund it but you just want to see the A1. How do you then score this? How do you vote on the question?

DR. GERSON: Well, to each our own. My perspective on that is you can use this in two ways. Like an A1, you can force a resubmission by a no vote. Different from an A1, you can ask Program to take care of details because the main essence is done, and, in fact, that's what the FDA would do, is take this cumulative discussion, since we are not really doing more than simply supporting and advising in a public forum, the perspective that the FDA will itself

develop. And so we are simply advising on a process that is the FDA's.

So if you have one level of comfort, you could say I'm comfortable that we've provided the information and the FDA can figure out the details. On another, you'd say wait a minute, I've got enough anxiety and concern here that there's real safety issues that we need to see this again.

Dr. Drake.

DR. DRAKE: No.

DR. BURKE: Could you state the exact question? We're voting on these three questions. Do the data demonstrate safety?

DR. GERSON: Correct. Do the data demonstrate safety for the proposed indication, and we just heard the exact phrase of the indication.

DR. ALLEN: Just to clarify, I think it was brought up earlier. So I get the question. I understand the question, and I get the if no. But as you said, if we are generally supportive of something but feel that what we want is some specific recommendations that aren't to do labeling, is the

discussion we've had up until now and our opinions, which are in the record, I think, sufficient for the FDA or are we going to get an opportunity afterwards to say I voted yes, this is, however, what I feel should be clarified?

DR. GERSON: Yes. I'll promise that after we vote, --

DR. ALLEN: Thank you very much.

DR. GERSON: -- there will be two events. One is I would like to indulge you to then explain quickly what the essence of your vote was, and then I think we should query whether there are additional comments about the other two elements.

Okay. So not hearing other items, I'm going to have you turn off your speaker thing, Dr. Burke good, and then I think the committee has on its electronic device here a plus/minus and zero and they're currently blinking; my goodness.

Okay. So you all get to press just one of those, please. Notice that one in the middle is a zero and that presumably means and does state it means abstain. So you can do that. It will be tallied. It

will be shown. Our votes individually will be, I believe, shown, and then we can have a discussion.

So on your mark, get set, vote.

MS. DAPOLITO: Can I have the microphone?

The consumer rep does vote on this panel. Yes, I'm sorry.

Okay. I'd like to read the tally of the votes for the public record.

On the question does the data presented demonstrate safety for the proposed indication, there are six yes votes, zero abstain votes, and eight no votes, for a total of 14 votes.

For the record, I will read the votes, except for what color is what. I'm sorry.

Dr. Gerson yes. Dr. Allen yes. Dr. Drake no. Dr. Chappell yes. Dr. Newburger no. Ms. Rue yes. Dr. Woo no. Dr. Dubinett no. Dr. Snyder no. Dr. Olding no. Dr. Kwak yes. Dr. Burke no. Dr. Taylor no. Dr. King yes. And the industry representative does not vote.

DR. GERSON: Okay. So as I suggested -- and maybe it will actually be helpful to the FDA if we

actually try to have individual statements about how we came to our conclusions. And unless there's a vote, I might go last.

Dr. Allen.

DR. ALLEN: So I voted yes, and the reason for my vote is I consider that there is sufficient data to proceed with caution. I would, however -- and this is my caveat. I would like to see some biopsy data. I have no significant concerns, but I do think it would be very helpful to start prospectively looking at this as the company moves forward. So it's a yes, with more than just a labeling requirement.

I mean, I think the things we talked about labeling it for this specific indication, you can do whatever you can. But clearly the FDA doesn't have an enormous amount of power in that respect, but I think we need to get some data on what this tissue is, and that speaks both this is going to be important and with my vote on efficacy.

DR. DRAKE: Well, I voted no, and I voted no because I think it's just insufficient. I think the data presented to us was very nicely done for the

limited amount of data that was presented, but I think it was superficial at best. I think we don't have any clue what this will do in other locations. I don't think we know what's happening. It's theoretically possible that we could inject something in a 20-year-old and have a retraction scar in a year or two that we couldn't do anything about.

I just think that it's premature to approve this on a safety basis at this point in time.

DR. CHAPPELL: I voted yes, and my reasons and concerns echo Dr. Allen's.

DR. NEWBURGER: I voted no, because I think the data are too short-term considering that this is living tissue without characterization of the effect there. I'd like to know that it's self-limited.

I think a biopsy series are absolutely necessary. And because of my concerns about this type of procedure for the indication, it's going to be used for purposes you have no idea. So I really need to see more definition of what it does.

MS. RUE: I voted yes for the same reasons as Dr. Allen.

DR. WOO: I voted no for a couple of reasons. First is that I'm not a dermatologist, but my thinking is affected quite a bit, significantly by our dermatology colleagues who have expressed a lot of reservations or additional data they would like to see before they will come forward and support it.

My other concern is that this is a novel product for cosmetic reasons and we really should exercise a lot of caution. So it is not that the sponsors have not provided -- have shown anything about the product that it's not safe, but to my mind, they have not demonstrated sufficient safety for the indication.

DR. DUBINETT: I voted no because of the issue of our lack of knowledge about the long-term outcome.

I do believe it would be constructive to know biopsy results, but, in essence, those biopsy results won't give us the information about long-term outcome, and that's what safety is. And so in my mind I think that's the key, the missing element.

DR. SNYDER: I voted no for the exact same reasons that Dr. Allen voted yes. It's just I wanted

to prevent -- I think the data that's missing are so easy to obtain and are just a minimal level of data that any transplantation study would require, and I simply wanted to prevent a runaway train. I still wanted to have a little bit of control over what's going on for the reasons that Savio mentioned.

This is really going to be very, very important and we just need to get it right. So it's a provisional no. I think once I know the data, I'm sure it'll support all of my comfort with what's going on.

DR. GERSON: Dr. Rao, would you like to comment, even though you didn't vote?

DR. RAO: Actually, I agree with the comments already made.

DR. GERSON: Dr. Olding.

DR. OLDING: I voted no, primarily because of the lack of knowledge about the mechanism of action. It's very difficult for me to get from A to B unless I know what A is. So that's the primary reason.

They have presented, I think, a wonderful packet of information, beautifully thought out, but there's just enough of it.

DR. KWAK: So I voted yes for the reasons I stated previously. Basically, in my opinion, the data that were available from the pivotal trials, in my opinion, demonstrate safety.

I should add, in terms of the mechanism of action, I'm a scientist myself, so the question burns within me, but I need to point out that there are many drugs, especially from my own experience in oncology, like Rituxan, for example, that we still don't understand why that works. So I think it's secondary.

DR. BURKE: I voted no, but, first of all, I think that the product itself is very exciting. I think we all want it. It's just that I think that, first of all, we must absolutely know in vivo the fate. And I agree with Dr. Snyder that it's not so difficult to do those tests.

The other consideration is this is a precedent, that this is going to be the second cellular technology that exists. We have no idea in this room what novel uses will be found for this product within a year or two of when it's on the mass market, and I can think of about five right now immediately and I think

we all can think of lots of things.

So, first of all, we all want it, other specialties will want it, but we have to have a precedent of a very high bar because it's a cellular technology and, the second, it might be approved, and because it has so many implications.

Finally, the long-term data, I'm sure, is available because it's very rare to have a product that has been used in humans 14 years ago and somehow there must be a way to go back to some of those patients and accumulate the kind of data that would answer some of our questions.

DR. TAYLOR: I, like Dr. Snyder, voted no, but it's a provisional no. I think the safety data are reasonably strong, but I would like to see the types of things I mentioned earlier, karyotypes, cell P21, P16, P63, surface markers. I'd like to see some of the biopsy data, and I'd like to understand the safety of this in populations beyond those age 40 to 65.

I think the safety data that we saw really are for that patient population for the most part. I agree there were some 23-year-olds in there. I also

understand that this will set a precedent, and I care very deeply about this field. And it's always difficult to be the front-runner, and sometimes it means the bar is slightly higher, but I think those data are fairly easy to get. And, ironically, I think I'm probably more comfortable with efficacy than I am completely with safety right now, and probably the vote will show that.

DR. KING: I voted yes the simple reason, going back to my father who said be sure you know who in the room is the 800-pound gorilla. And in this sense, the FDA is asking us as an advisory group to give them input so they can make a decision.

I'd like to make the point what additional studies should be done? Everybody's giving a provisional yes or no, but based on we don't know certain things. So it's up to this advisory committee to come up with what kind of additional studies need to move this bar forward so that the FDA can make that kind of decision.

I think that given it's been around for 14 years and it hasn't killed off people or a lot of

lawsuits seems to be that it’s met the test of time that way.

Having worked with epidermal growth factor from almost its discovery-type thing, you find out, if not by 20 years, you find out it works in cancer and so forth. So I’d like to see this product move forward and the FDA decide from our input what studies we as experts should insist or suggest, rather, should be done.

DR. GERSON: I voted yes, and I agree with a number of the discussion points, with Dr. Allen that the product appears to be safe. It passes my sniff test for safety. I really can’t find a serious linkage between adverse events, other than short-term injection-related phenomena, and appears to be significant.

I agree with the concerns about needing to understand a mechanism, needing to understand fate, needing to understand long-term events. But in the biologic world and in the cell world, we’ll spend the next 30 years trying to figure out what, why, and how these cells work, just like we don’t understand them in

our own bodies.

So I was comfortable that there had been adequate clinical experience to demonstrate safety. I wish there had been more research and development into the mechanisms of that safety.

So Dr. Witten has a comment.

DR. WITTEN: No. I have a question, actually. I've just heard a number of comments about additional studies and I would like some clarification, particularly from the dermatologists on the group who mentioned wanting to understand longer-term outcome, whether they're referring specifically to biopsy studies or clinical outcome studies, because those are really two different things, and I think we've heard from other members on the AC of that.

So, in particular, Dr. Drake and Dr. Newburger and others, if you can comment on what type of longer-term information, is it mechanism information that would give us some idea of what might happen in the longer term or some idea of how long to follow patients or a longer-term clinical outcome study, and, if so, what specifically would we be looking for?

DR. NEWBURGER: Dr. Witten, those are two very good questions.

First of all, I believe that I can speak for the three of us here when we would like to know what is happening in the first six months or so. Are we seeing normal collagen production? Are we seeing scar formation?

I only saw in the references one comparison histologically from post-auricular implantation from Dr. Boss, but I couldn't really tell what the effect was in terms of comparing collagen just on a pathology basis because the magnifications were different.

So I think that we really do need to know is it normal collagen, is it scar formation. And in terms of longer-term studies, I think that that may not be necessary beyond a year, if the characterization of whether the fibroblasts are living and productive is defined. Then we'd have some idea of what we could expect longer term. So you wouldn't have to follow it 20 years before the clinical evidence is there.

DR. DRAKE: I think you guys know how I feel about biopsies. I think we have to have that. That's

a short-term thing that would give us some information.

I think we need some information, I would like some information, on some other sites because the nasolabial folds are a pretty safe site to do almost anything in, and we've known from other products that, depending on where you inject something, you can get different results, and some of them are devastating.

Even though wrinkles are "kind of wrinkles," I mean people tend to dismiss them, the problem is if you inappropriately treat them in some areas, you lead to really bad things, like blindness or neurologic impairment. I mean, there can be all kinds of things that happen. Even though it seems like a trivial or minor condition, if we don't know what we're doing and where we're doing it, you can end up with some serious consequences. So I think we need to see what happens and I'd like to see some studies on other sites and what might happen there.

I think another thing -- I was interested in -- Lloyd was one of my professors, so I hate to always -- I don't want to disagree with him very often because I usually lose on that deal. But I would tell

you, Lloyd made the comment that he thought that we haven't heard about lawsuits and all this stuff. I don't think that's relevant.

I mean, all kinds of stuff happens out there and there's no way of really reporting it. It's not well followed. We don't really know what happened in Europe with these.

The question is does the company know? Is there data out there that they could mine to give us some answers on what their long-term knowledge is? I didn't see a single thing up there -- and maybe I missed it, but I didn't see anything that they'd looked at 1,200 patients or a 1,000 patients they mentioned were out there, but they didn't tell me what the side effects, if any. And there may have been none, which would have been very important for me to know, but in fact I don't know that.

So I think that some of the long-term data that's potentially there, potentially, if it was possible to mine, that would be great. And then I think, also, I think some of these markers -- the cell guys at this table are much better than I am, but I

think there could be some wonderful studies done on a really short-term basis because they know far more about that than I do.

But as a dermatologist, I can tell you we have seen drugs out there, products out there, that we've used, and a year or two down the road, we've seen some serious side effects. And probably one of the more famous ones, believe it or not, you've all heard about, and I'm going to mention one at the risk of being killed, but I've been on the Accutane panels ever since this all started. And when it first came out, it was the panacea; it was the best thing since sliced bread. And then over time, we've learned the side effects and the sequela and the consequences. And I just think you can't be too superficial.

Finally, I always look at the risk-benefit ratio. If I was a lymphoma guy, like my buddy across the hall there -- my dad had mycosis fungoides, okay? Now, if I was sitting there with a mycosis fungoides patient who's got tumor stage and there's nothing left to do, I'd probably be the first one to say let's approve this, let's run to approve it because there's

no other options and the benefit could potentially outweigh the risk. This is the reverse. A wrinkle is not going to kill somebody at this moment, and I think we have time to try to figure out what we're doing.

Then, finally, I'm going to comment on the notion of burns.

Let's face it. We've got some real potentially exciting areas in which this product could be used, there's no doubt about it, but I think we have to know more about it because the second it gets out there, people are going to be injecting burns, they're going to be injecting keloids, they're going to be injecting everything in the whole world, not on location, but they're going to inject different things. And I don't think we know enough to turn it loose yet. And, trust me, the dermatologists at this table all know the second something gets out there for wrinkles, it explodes. I mean, it just becomes huge.

I wrote one paper at one time on cosmetic strength of alpha hydroxy acids, and do you know that that hit the front page of *USA Today*, I mean it hit ABC News. It was huge. I mean, the whole notion of

wrinkles and aging skin is huge. It will generate tremendous excitement. And I don't think we on this panel, at least me, and I'm not sure that the agency, wants to be in a position of not having indepth answers because, trust me, there will be people who will ask for indepth answers and I don't have them at this table yet.

So those are my comments. I think much of this information could be gathered rather quickly and rather easily. I voted against it because I don't want to turn it loose until we have some of those answers, but I'm not voting against it because I think there's great potential but I think it's premature.

Sorry. That was a long answer, Mr. Chairman. I apologize.

DR. ALLEN: I've just got one comment in that regard. My yes vote is tempered by the fact that at the end of the sentence is the statement for the proposed indication.

So I have looked at it in the context of nasolabial folds only. If we're going to get into discussions about what happens if you apply it at 14

sites around the face, I have different considerations. So I just want to be clear. In the proposed indication, I feel it. That's my vote.

DR. GERSON: Have we answered your query to your satisfaction?

DR. WITTEN: Yes. Thank you.

DR. GERSON: One more comment from Dr. King.

DR. KING: I'm not going after Dr. Drake. She always likes to tell me about it. But the answer is there's lots of data that says that fibroblasts from different sites have different parameters. They grow differently. That's why you've got eyebrows. That's why you got a lot of other things. It's called donor site dominance.

So there's apples and oranges here. There's a difference between taking a biopsy from the face, behind the ears and putting it on other parts of the face, but to take this product, which, depending on how you do it, would be at another site, it's like having an undescended testes and getting cancer. It's not abnormal tissue, it's just in the wrong site.

So my point is that I was voting on the basis

of this indication and saying, with the proviso, that the FDA is going to take this advice and tell the company what they think meets the criteria for safety and efficacy of this committee and their own studies.

So I trust the FDA to do what they think is in the best interests of the public.

DR. SNYDER: One of the reasons -- some of the studies that we are talking about may even address not just mechanism but even safety.

I think there's a very good chance that these cells are not even surviving. I think we've started to learn, for example, in the mesenchymal stem cell field, and Stan can speak to this, that sometimes the mesenchymal stem cells don't even hang around a long time. They do what they need to do, which is quite important, and then disappear.

If these cells do a hit and run and then disappear, then even some of the safety issues, other than how they change the environment, are not going to be pertinent. They're not going to be hanging around to make neoplasms.

DR. GERSON: Yes, Dr. Drake.

DR. DRAKE: There's one other thing. This is going into an area of motion. And if you look at wrinkles, a wrinkle on my forearm is a totally different animal than a wrinkle on my face. And so you inject something there and just the repetitive motion will change the architecture of it over time. And the fact that this architecture apparently withstood over time is what made me worry is this a scar and not actual biologic effect. And that relates to just what you said, that these cells sometimes hit and run.

I don't even know if there's any viable cells there, but we do have to remember that this is in an area of motion, of facial motion, and when you have that, the lines and furrows tend to keep coming back, and I don't know that you have indefinite -- if you have indefinite action of a fibroblast laying down a new matrix, that would be terribly exciting, but I don't think that's what's going on here. We just don't know, though.

DR. GERSON: I would like to keep the enthusiasm of the discussion, and, therefore, my hunch is we should go on to question number 6. Thank you.

So this relates to effectiveness. The section in the Provision 21 CFR 601.25(d)(2) states that "effectiveness means a reasonable expectation that in a significant proportion of the target population, the pharmacological or other effect of the biologic product, when used under adequate directions for use and warnings against unsafe use, will serve a clinically significant function in the diagnosis, cure, mitigation, or treatment or prevention of disease in man."

Do the data presented demonstrate effectiveness for the proposed indication? We will discuss, then vote. If no, what additional studies should be performed? Discussion. If yes, do you have any specific recommendations for the labeling? Discussion. And as with the prior question, I would ask that we discuss all three components, at least in general, and then we'll vote. And we've asked Dr. Olding to help us frame this question.

DR. OLDING: The pivotal studies for this particular product have demonstrated a statistically significant superiority over the vehicle control in

both the co-primary endpoints, and they're also supported by the secondary endpoints.

But in the Phase III-A study, it failed to show statistically significant investigator improvement, and in the subgroups of the pivotal studies, the responder rates which were, remember, two changes, were very different, 33 percent in 005 and 19 percent in 006.

So I think it has, in fact, demonstrated efficacy for the proposed indication, which is treatment of a nasolabial fold wrinkle, not the nasolabial fold but the nasolabial fold wrinkle.

But if you'll look at the question, it says in a significant proportion of the target population and it also asks if it will serve a clinically significant function. That portion's a little bit more difficult for me to answer.

Some of the photographic documentation that we've seen, I think everyone has some questions about, particularly since the change photographically to me was minimal. We also don't have a lot of information about the aging, particularly the aging male, black,

smoker population in terms of effectiveness, the effectiveness of repetitive injections beyond the three, because, undoubtedly, as we've heard before, if this gets released, it certainly will be used in more places and more times than any of us can imagine.

So we don't know about effectiveness; will it be used off label for volumizing? And I really would like to see perhaps a better way of photo documentation of the effectiveness. But it was not compared with one of the fillers, one of the other approved fillers. Appropriately so, I think, because I think it's not meant to fill up something.

When we think of fillers, we don't just think of filling up a very superficial wrinkle, and there's a big difference between a wrinkle and a fold. The trouble is, even in their documentation, they suggested that it improved not only wrinkles and folds but also, because of some of the previous ones, contour improvements. It has nothing to do with contour improvements, in my opinion. And certainly in terms of labeling, I would want to make certain that the labeling reflected only improvement in wrinkles, not in

folds, and not in contour.

Those are my thoughts.

DR. GERSON: So could we go around? Will you allow me to encourage that?

Dr. Kwak, you're right up.

DR. KWAK: So I agree with most of those comments. I think the study met its primary endpoint. This is supported by the intent to treat analysis and, even more convincing, the modified intent to treat analysis. So I believe the data do demonstrate effectiveness for the proposed indication.

DR. BURKE: I think the limited data do show some effectiveness, but, again, when we talk about significant function, we don't know what these cells are doing. We don't know their function. We don't know if they're viable, if they're multiplying themselves, if there's some subpopulation of some karyotype that happened to proliferate more in vitro from the population of the biopsy, and we don't know what's being synthesized in the long-term histology. We don't know the effects of the inflammation from any injection, let alone this.

So it looks very, very promising. We all want it tomorrow, but we should just find out the function physiologically by sequential biopsies; and, again, try to glean data from the people that had it 14 years ago and five years ago.

DR. TAYLOR: I actually think the efficacy data are fairly convincing, enough so that I wish it were a product that were available today. And I can tell you that we talk about this as if it's trivial and doesn't really matter. We say it's a wrinkle, but there's a huge need for cosmetic improvements for people with -- some of the acne scarring data we saw today, some of the other cosmetic indications really suggest to me that there's a huge potential here for this product going forward.

I personally am much more comfortable with the efficacy data than I was with the safety data, so saying that, I'm hard-pressed to have a negative at this point.

I guess the one thing I would ask is I heard you say you replotted some data earlier at lunch, you, Rick.

Could you clarify for me again what those data said with regard to evaluator and site and whether or not it spoke to the efficacy?

DR. CHAPPELL: Yes. There seems to be some evidence that there are good sites and bad sites, that some sites are consistently low, that is, consistently meaning the treatment and control groups are both low and some are consistently high.

By looking at those same data by subject evaluations, it seems that you can attribute the goodness, so to speak, of those sites to the evaluators; that is, there's no evidence that the --

DR. TAYLOR: The goodness or the badness?

DR. CHAPPELL: Well, it's two sides of the same coin.

DR. TAYLOR: No, serious question.

DR. CHAPPELL: Some sites look better, apparently, because the evaluators seem to be liberal in attributing benefit. Some sites look worse because in part, at least, the evaluators are tough sells. There is no evidence at all that efficacy varies across sites that I can see.

DR. TAYLOR: And I guess the question really was, were the patient evaluations more consistent with the good data or the not good data?

DR. CHAPPELL: They were more consistent with each other; that is, they were more constant. They didn't vary as much, and when they varied, it had nothing to do -- the treatment group --

DR. TAYLOR: But the efficacy was still there?

DR. CHAPPELL: -- had nothing to do with the control. But the efficacy was still there. You just didn't see the pattern that treatment and control varied in tandem. So it is relevant to the training of evaluators for future trials.

DR. KING: I'm also very comfortable with efficacy. My training as an engineer initially was with the concept of black box. You put something in, it goes through a black box and some miracle happens in the middle and then you get an outcome.

I think this is about where we are. We've got some efficacy. I like some kind of outcome that's successful that defies the ineptness or the underrating or whatever on the part of the group of clinical

studies, but nonetheless the analysis to me says that it does, as an outcome of the other side of the black box, work. I'm still worried about what's on the inside, as other people expressed, like we need more data. But having worked again with a lot of other compounds, sometimes it's 20 years later, you find out what it's results are and I'm favor of the efficacy being substantiated.

DR. GERSON: My perspective on this is that there is demonstrated effectiveness for the proposed indication as narrowly defined by the sponsor and by the question, but it falters somewhat on the parsing out of the previous phrase, the previous sentence which is, "will serve a clinically significant function in the diagnosis, cure, mitigation, treatment or prevention of disease in man." And although the sponsor suggests an interest in disease, and we've heard an unmet need, I don't quite define the unmet need as a disease. And so I'm struggling a little bit with just how carefully to parse out the focus of the agency towards disease, although it certainly manages cosmetics as well. I think, in general, the

effectiveness in the limited scope is there.

DR. WITTEN: We didn't intend to focus on the term "disease" since these wrinkle treatments are something that we regulate.

DR. GERSON: So a human condition perhaps.

DR. WITTEN: Yes.

DR. ALLEN: So I think I'm in general agreement. I actually feel reasonably comfortable, and this is something that we have a measure of. In the short term, I think that there is demonstrated efficacy.

I guess my concern, if I have one, with number 6 is this concept of a significant proportion of the target population always brings me to think about the concept and difference between something that's statistically significant and something that's biologically significant. And so I think of a 33 percent success rate as a 67 percent failure rate because that's just my natural personality to be a bit pessimistic apparently.

But I guess ultimately, though, it really isn't my agreement because if this works and patients

like it and clinicians are comfortable with it, it will sell, and if it doesn’t, they will falter out. So I guess on balance, the data I’ve seen support for me the efficacy in this specific application; although I always have a tough time thinking it’s efficacious without really understanding what it’s doing, but it is meeting the goal of improving the visible appearance of these wrinkles. So for me, it’s relatively straightforward.

DR. DRAKE: Well, I have a hard time voting for anything on efficacy that I have trouble with on safety because I don’t know what the long-term things are.

I also think -- and I agree totally with Dr. Allen, his remarks about wrinkles versus folds versus contours are essential. And this question, question number 6, doesn’t say nasolabial fold wrinkles; it says it’s broader. And so, I just don’t think it’s met that standard for broader. I mean, as a matter of fact, I’m not even sure it meets -- I don’t know. I think it’s premature.

Thank you.

DR. WITTEN: The proposed indication is treatment of moderate to severe nasolabial fold wrinkles in adults.

DR. DRAKE: But in question 6, it doesn't say that.

DR. WITTEN: It just says proposed indication.

DR. DRAKE: I still stand by I think it's premature. Thank you for the clarification.

DR. CHAPPELL: What's been said has made perfect sense to me. I have a comment on what may seem an arcane point, so I'll keep it brief, but it's important because I think we dodged a bullet here.

Forty-nine patients, that's 12 percent of the total patients in the two pivotal studies, didn't show up for their first treatment. And various analyses were done. And even the worst case -- which I think is pretty extreme, where you say everybody in the treatment group who didn't show up was a failure and a success in the control group. Even the worst case scenario had the effect on the right side from the company's point of view. So it hasn't been addressed much here.

But suppose the next biologic is for a more severe indication, and suppose the effect is not p less than .0001, I forget how many zeroes, lots of zeroes. Then what we'll do is spend a lot of the afternoon, you'll spend a lot of the afternoon glaring at me and the other statisticians while we confuse you horribly and it won't be clear at all.

So the cause of this problem is that, unlike drugs which can be conveniently randomized immediately before the patient gets it -- so most drugs, there won't be anybody or very few people who don't get one treatment. Here it takes a couple months?

How long? A couple months; 90 days, all right, so three months between the biopsy and the treatment. It is awfully tempting to save all that money and not generate the treatment for half the patients, and then it's called modified intent to treat.

It did not bite us here, but my request to the FDA is that they develop guidelines as to when that's acceptable and when, if ever, they should make the drug for everybody and randomize just when the person sits

down for the injection because in a future meeting it may be much more problematic.

DR. NEWBURGER: I was impressed with efficacy in terms of the subjective assessment. I think that the numbers of individuals who ranked themselves as responders were really impressive in both studies. And in light of the fact that it is very difficult to have objective evaluators appropriately trained, I think that that's significant for efficacy.

DR. GERSON: May I just ask, because I've sort of been brewing on this, as a dermatologist, is this a purely visual cosmetic event for the patient or is there some physiologic component?

I realize it's cosmetic. Is it purely visual? Is there a tautness? Is there a feel of the movement?

DR. NEWBURGER: When someone says that they have a good response, they usually are assessing themselves not in a static fashion but when they animate. So it's not only how they look when they're just looking in the mirror but really also how they feel when they're interacting. And it may have some impact in terms of tightness of the tissue.

Of course, a lot of it in terms of someone -- you don't think so?

Well, that's been my experience with other fillers. Okay. Well, how people feel that they're perceived by others, also, and how that interaction occurs.

MS. RUE: I think it proved its efficacy for the nasolabial folds in the population group that it was mostly tested on who really probably didn't need it yet, and I think it needs to be looked at for the other population groups that were under study.

DR. WOO: I think the study has demonstrated convincingly efficacy in terms of one primary endpoint. The subjects of self-evaluation is very impressive, and after all, that is the most important endpoint because you're going to sell the product to the subjects, and if they think they improve, that's very, very important.

My concern has to do with the evaluators' assessment. I've said this before. So in the absence of objective data, we have to then look at subjective opinions. And among the objective opinions, I look at

006. You have three sites that are very, quote unquote, “good sites,” and then three sites, quote unquote, “under-performing sites.”

So I’m not trying to do a subgroup analysis here. I’m not a biostatistician, but the results led me to question the validity of the assessment in the co-endpoint. So if one group of evaluators could be so different from another group of evaluators in terms of outcome, it causes a great doubt in my mind whether that assessment is legitimate to begin with.

So until that concern of mine can be addressed, I don’t think the co-endpoint has been met.

DR. DUBINETT: So in my mind, I think it’s important for me to answer directly the question that is here on the page, and it’s clear from the data presented in my mind that they have demonstrated effectiveness for the proposed indication.

DR. SNYDER: I’m pretty comfortable with the effectiveness, particularly for the population examined, which is mostly non-elderly Caucasian women. I think we’ve already indicated that we’d like to see studies of some potential patients that don’t fall in

that category. However, if someone not in that category decided to use this procedure and did not get a great outcome, I'm okay with that, as long as it's safe.

I think that there is, as I suggested earlier in the day, a very easy way to rule out evaluator difference or bias versus site performance simply by taking the photographs and swapping them or having outside reviewers also grade the photographs. That's about as objective data as we're going to get in lieu of having computer modeling.

I think it is also very interesting and compelling that the patients themselves across sites, regardless of what the evaluators said, believed that there was efficacy. And while one could say, well, that's a placebo effect, I still don't think it can be discounted, not only because they felt better and they felt that there was efficacy, but also patients tend to examine themselves in a way that professionals do not. They key on things that are important to them that may not have been part of the criteria, and that has to kind of be considered in terms of the overall efficacy.

So I feel fairly comfortable with the efficacy as demonstrated.

DR. RAO: I agree for the specific application that's requested, and for the specific answer to this question, I think they demonstrated effectiveness.

DR. GERSON: Dr. Olding.

DR. OLDING: Would you like me to summarize what I think the group said or would you like some more comments?

DR. GERSON: Well, you've now heard the group, so why don't you provide your own comments and then a summary?

DR. OLDING: Well, as I said before, and as has been echoed by the majority of the members of the panel, I believe that the majority feel that in fact it has certainly met the expectation that it is effective within the limited parameter of the test, and that I believe is really important.

This is a wrinkle, and a wrinkle is not anything but a wrinkle. It's not a fold. It's not a contour deformity. So we have some people who are concerned about the validity of the evaluation methods,

but I think the majority of people are comfortable with them, in part, because they know there aren't any others available beyond what we have now. So, again, within the limited scope, I believe that the majority of people seem to be comfortable with it.

DR. GERSON: I'd like to move the group towards a vote and suggest that we would have some time to come back to the other two components of this question for further comments on them.

Are there other key issues that one would like to present or comment on? If not, why don't we go ahead and vote. And so it's the same routine as we just did before. So go ahead and vote your conscience, if you could.

MS. DAPOLITO: There are a total of 14 voting members. Eleven members voted yes, three members voted no, zero abstained to the question do the data presented demonstrate effectiveness for the proposed indication, for a total of 14 votes.

I will now read the individual votes. Dr. Snyder yes. Dr. Dubinett yes. Dr. Woo no. Ms. Rue yes. Dr. Newburger yes. Dr. Chappell yes.

Dr. Drake no. Dr. Allen yes. Dr. Gerson yes. Dr. King yes. Dr. Taylor yes. Dr. Burke no. Dr. Kwak yes. Dr. Olding yes.

DR. GERSON: So if we could go around one more time, I'll again start with Dr. Olding to provide us his specific rationale for the yes vote on demonstration of effectiveness for the proposed indication.

DR. OLDING: I voted yes, but it's a qualified yes. I would want very specific documentation in the labeling, et cetera, about what it was approved for, not so much even location, because I think people will use it off label as they will when it gets approved. But I believe that it's important that somewhere it indicates that we have no efficacy data beyond six months, that it's used for wrinkles, that it describes what a wrinkle is, and that it indicates that we don't have, at least at this time, any additional data on indications of use in multiple areas. And, of course, I would hope that additional studies would be done regarding it even before it was released.

DR. GERSON: Dr. Kwak.

DR. KWAK: I voted yes, and I would just, again, encourage the FDA to consider whatever it means it has to explore new mechanisms for post-marketing regulation of off-label use, especially for an autologous product because, again, this is something that's a unique situation. It's under your control, under the sponsor's control, the distribution of it and the use of it.

Then I also wanted to just echo Dr. Chappell's comments about the modified intent to treat. Again, the unique value that that kind of analysis might have for biologic products, where it takes time to make the product and this is not a drug off the shelf. So I would just encourage the FDA to explore both those issues.

DR. GERSON: Dr. Burke.

DR. BURKE: I voted no, again just because I want more data and I think the idea of having evaluators from many sites all evaluate all of the pictures because then I think that it would be, first of all, statistically stronger data and far less subjective.

I think patients, if they're treated in a complementary, you know, without paying for wrinkles, they're going to be more apt to be optimistic about their treatment, which is not to say it doesn't work because any six-month improvement is, as Dr. Newburger said, quite impressive.

So I think that what was presented today was preliminary data, and I know the question said clinically significant function. But when I see the word "function," I have to know more than just a clinical level, a clinical observation from some photographs.

DR. GERSON: Dr. Taylor.

DR. TAYLOR: I voted yes, with the understanding that we're talking about, again, the population in which this was mostly tested, and I think the efficacy data were not as strong for individuals above the age of 65 and that labeling should potentially indicate that.

DR. GERSON: Dr. King.

DR. KING: I guess beauty is in the eyes of the beholder and perception's reality. So it is hard

to fool that many people all the time. So I came down on the side of the efficacy; that many people thought it was going well, I was in favor of that.

I have the concerns of other sites and other ages and whatever, but on this question, I had to believe that the efficacy, particularly on the patients' feedback, is something that has to be considered and should be in a lot of other type studies where the treatment's done and there's no feedback from the patient.

DR. GERSON: I found this to be efficacious for the indication, and I'm concerned about, as others have mentioned, individuals over the age of 65 and the effort by both the agency and the sponsor for looking at other indications.

DR. ALLEN: I voted yes, and I'd echo the previous comments. The other thing I'd say is that this was done with a prescribed dose. Even though this was a dose range, this was a prescribed dose. The one thing that is true is that the sponsor is going to produce a certain number of cells and there are concerns that when the physician gets that, he or she

could dilute that down and do more sites. So I would want to see in the labeling a prescribed information about the number of cells. It should be within the dose range that was tested. So I think that's important.

I don't know what the FDA can do about that, but that would be my recommendation, is that there is a dosing, and I think that will take care of at least on the occasion it's injected, that it's only really going to go in one site. There's a limit to how much that can be injected. It should say something like that, I think.

DR. DRAKE: I voted no for a variety of reasons. One, I can't vote yes on efficacy on any drug that I'm convinced of the safety of. It's just a fundamental principle I have.

The second thing is I think that there's a burden on the FDA -- with all these comments I've heard, it's not supportable. I mean, the FDA has a certain amount of ability to do things, but there are limited resources, staff, et cetera, in terms of monitoring all this stuff. And I am frankly concerned

that this study was too superficial.

I mean, we're approving a second drug in a class that has -- we're looking at one wrinkle on one face. I guess maybe my fundamental issue is with the way the question was posed. I think it's inappropriate to approve a drug that's limited to one wrinkle on the face that has potentially wide ramifications, and I think we've opened Pandora's box.

DR. CHAPPELL: I voted yes, but I have no further comments.

DR. NEWBURGER: I voted yes, and I'll make up for Dr. Chappell. I voted yes primarily on the basis of the subjective overwhelming response.

I think that this is a very narrow limitation. I think the nasolabial wrinkle is a very limited location. If there was some way truly that the site of injection could be controlled until such time as further studies showing the safety, the mechanism of action were available, that would be ideal.

One thought is in terms of dilution, because that's a very valid point, and we certainly see that once a product is out there, there is product

adulteration in all kinds of ways by practitioners. So perhaps there would be a syringe mechanism that could not be altered, that didn't have a luer lock, and that was unique, that you couldn't add something back to it.

I think that it is really important to do further studies showing what the difference in terms of effectiveness is on different levels of the injection. I understand that this is easier to standardize because it's placed more superficially in the papillary dermis. It's easy to see a weal, visualize in someone who's fair-skinned the tip of the needle. But I think that there really does have to be, as part of the characterization, a mechanism of action, what's happening to these fibroblasts.

Lastly, I don't think that a retrospective analysis of all the photographs that were taken as a secondary endpoint is going to be valuable because they do have different lighting baseline and post-treatment in many of them, and the positioning, the angle of the subject is different. So you can't really see what's going on. But I did vote yes.

Thank you.

MS. RUE: I voted yes because I thought it proved effective for the proposed indication.

DR. WOO: I voted no because I lack confidence in the validity of the evaluator's test as a co-primary endpoint analysis.

DR. DUBINETT: I voted yes because I thought the data supported the effectiveness for this proposed indication. I agree with the comments of others, including Dr. Olding and Kwak, regarding the age group, potential age group restrictions, and also Dr. Kwak's comments regarding looking to the future in order to create mechanisms in which we would be able to have control regarding autologous products and their use.

DR. SNYDER: I voted yes, but with the caveats that have already been mentioned. I think the labeling should reflect that and say something like not proven efficacious for those over 65, smokers, non-Caucasians, and sites other than nasolabial fold wrinkles at the prescribed dose.

As just a note to the FDA, I really would think it would be valuable to have as objective as possible the photographs evaluated, as Dr. Burke

mentioned, by some other observers and graders, either swapping at the sites or those not even involved in the study, other dermatologists, to grade the data.

DR. GERSON: Dr. Rao, could I ask you for comments, as well?

DR. RAO: No additional comments.

DR. GERSON: Well, we have in fact, I think, managed for the most part to give some good suggestions on additional studies and on recommendations for labeling. Unfortunately, I did allow ourselves to reinterpret those questions for discussion, so we discussed both of them, even if yes, if no.

Are there other comments on those two topics that members would like to make?

Dr. Newburger.

DR. NEWBURGER: One comment is no practitioner reads the label. So any direction in terms of how the product is used really does have to come from an external control mechanism, whether it's FDA, whether it's the sponsor. Nobody reads the label.

DR. GERSON: Dr. Taylor.

DR. TAYLOR: I would recommend that, given the

small number of non-Caucasian patients and patients over the age of 65, that a registry be kept going forward of race, ethnicity, age, sex, so that data can begin to be gathered in a de-identified manner, based on those criteria.

DR. GERSON: Dr. King.

DR. KING: I propose a study based on the fact that people are worried about whether the fibroblasts die off, and one assumption is either it's volume or it's the supernatant. And so, spinning down the cells and having the culture media supernated, injected at the appropriate times would serve the same purpose of insulin for diabetics who have minimal pancreatic function.

So if you're really worried about the cells are putting out the right stuff, why don't you let them put out the stuff and leave them behind and inject the supernatant?

DR. GERSON: May I ask the FDA whether there are other questions or issues you'd like us to address?

DR. WITTEN: No, and I'd like to thank the advisory committee for such a comprehensive discussion,

and especially thank you for chairing this meeting.

DR. GERSON: Thank you. If there aren't other comments, I think we can adjourn.

I want to thank the FDA for its presentation, the sponsor for its presentation, the members for its discussion.

Thank you.

(Whereupon, at 4:56 p.m., the meeting was adjourned.)

CERTIFICATE OF REPORTER

I, JANET EVANS-WATKINS, do hereby certify that the foregoing proceedings were taken by me and thereafter reduced under my direction to typewritten form; that this transcipt is a true record of the proceedings; that I am neither counsel for, related to, nor employed by any of the parties to this action; and, further, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of the action.

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JANET EVANS-WATKINS

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